Introduction

Fluorination is a very useful strategy in the design and synthesis of bioactive compounds, since the special nature of fluorine can confer enhanced binding interactions, metabolic stability and desirable physical properties to a molecule. In fact, approximately 5–15% of the total number of drugs launched in the past 50 years were fluorinated compounds and this percentage has noticeably increased in the past five years.1 Recently, a novel deoxofluorinating agent, 4-tert-butyl-2,6-dimethylphenylsulfur trifluoride (named Fluolead™, 1) has been reported.2,3 Fluolead™ is a versatile reagent with relative high thermal and hydrolytic stability that fluorinates a broad range of substrates, generally more efficiently and selectively than currently available deoxofluorinating agents, such as diethylaminosulfur trifluoride (DAST), Deoxo-Fluor™ and other related reagents.2,3,6,14 In addition, it can be obtained from commercial sources or be easily prepared in two steps from commercial available 5-tert-butyl-m-xylene (Scheme 1).2,5 Because it is versatile, efficient, shelf-stable, easy-to-handle, and relative highly safe, Fluolead™ is expected to be widely used in both academic and industrial areas.2

Abstracts

(A) It has been reported that Fluolead™ reacts with alkyl and aryl ketones, aldehydes and keto esters producing the corresponding difluoro products in high yields.2,4 Umemoto and co-workers2 found that the deoxofluorination of cyclohexanone with Fluolead™ in the presence of HF-pyridine gives a 99:1 mixture of difluorinated product and monofluorinated olefin in 81% yield, being highly selective in comparison with DAST and Deoxo-Fluor™, which gives 2:6:1 and 1.5:1 mixtures in 79% and 94% yield.6 Fluolead™ efficiently fluorinates diketones and non-enolizable ketones under very mild conditions, while fluorination of such substrates with SF4, DAST and Deoxo-Fluor™ requires severe conditions or give products in low yields.4a

(B) Xu and co-workers developed a method to generate Fluolead™ in situ for the deoxofluorination of aldehydes and ketones.2 This method gives the gem-difluorinated products in good yields while problems associated with preparation and use of Fluolead™ are minimized and scrupulously dry reagents are not required.
(C) It has been reported that Fluolead™ can react with carboxylic acids to give directly the corresponding trifluorinated product in good yield, a reaction that was only carried out with MoF₆ or SF₆ as an extremely toxic gas.

(D) A highly stereoselective deoxofluorination of d-glucopyranose with Fluolead™ giving 96:4 mixtures of α- and β-fluoro products was reported. When the replacement is carried out with DAST or Deoxo-Fluor, 11:89 and 28:72 mixtures of α- and β-isomers are obtained.

(E) Stereoselective deoxofluorination of enantiopure alcohols is difficult to achieve, particularly if the alcohol is prone to S_N1 reactions as in the case of benzylic alcohols. It has been reported that reaction of benzylic alcohol with Fluolead™ occurs with high stereochemical inversion and lead to the fluorinated product with 92% ee.

(F) 4-Fluoropyrrolidine derivatives are useful intermediates in the synthesis of bioactive compounds, such as dipeptidyl peptidase IV inhibitors. The conventional method for preparing these derivatives from N-protected 4-hydroxyproline requires at least four steps. Recently, Singh and co-workers described a new methodology in two steps, using (2S,4R)-4-fluoropyrrolidine-2-carbonyl fluoride as synths, which can be synthesized in high yields by stereospecific double fluorination of optically active N-protected (2S,4R)-4-fluoropyrrolidine with Fluolead™. In addition, some 4-fluoropyrrolidines may also be prepared in a one-pot procedure by reaction of N-protected 4-hydroxyproline with Fluolead™, followed by reaction with an appropriate nucleophile.

(G) In an attempt to synthesize (2S)-2-(fluoromethyl)-N-tosylpyrrolidin-3-yl trifluoromethanesulphonate, Hugenberg and co-workers reported the formation of a 95:5 mixture of the rearranged fluoro piperidine product and the expected fluoro pyrrolidine in 95% yield. The reaction with Fluolead™ was found to be much more selective and efficient than most reactions described in the literature using DAST and Deoxo-Fluor.

References