Fluolead

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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-\(t\)-butyl-2,6-dimethylphenylsulfur trifluoride (named Fluolead\(^\text{TM}\), 1) has been reported.\(^2,3\) Fluolead\(^\text{TM}\) 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\(^\text{TM}\) 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-\(t\)-butyl-\(m\)-xylene (Scheme 1).\(^2,5\) Because it is versatile, efficient, shelf-stable, easy-to-handle, and relatively highly safe, Fluolead\(^\text{TM}\) is expected to be widely used in both academic and industrial areas.\(^2\)

Abstracts

(A) It has been reported that Fluolead\(^\text{TM}\) reacts with alkyl and aryl ketones, aldehydes and keto esters producing the corresponding difluoro products in high yields.\(^2,4\) Umemoto and co-workers\(^2\) found that the deoxofluorination of cyclohexanone with Fluolead\(^\text{TM}\) 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\(^\text{TM}\), which gives 2.6:1 and 1.5:1 mixtures in 79% and 94% yield.\(^6\) Fluolead\(^\text{TM}\) efficiently fluorinates diketones and non-enolizable ketones under very mild conditions, while fluorination of such substrates with SF\(_3\), DAST and Deoxo-Fluor\(^\text{TM}\) requires severe conditions or give products in low yields.\(^4,6\)

(B) Xu and co-workers developed a method to generate Fluolead\(^\text{TM}\) 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\(^\text{TM}\) 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-e, 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 SN1 reactions. It has been reported that reaction of N-protected 4-hydroxyproline with Fluolead™, followed by reaction with an appropriate nucleophile, 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.

(F) 4-Fluoropyrrolidine derivatives are useful intermediates in the synthesis of bioactive compounds, such as dipetidyl 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-tosylpyrrolidine from (2S)-N-tosylprolinol using Fluolead™, 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 or Deoxo-Fluor™.

References