SYNLETT Spotlight 386

Fluolead

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This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

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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-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride (named FluoleadTM, **1**) has been reported.^{2,3} FluoleadTM 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-FluorTM and other related reagents.^{2,3,6,14} In addition, it can be ob-

tained 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, FluoleadTM is expected to be widely used in both academic and industrial areas.²

Scheme 1

Abstracts

(A) It has been reported that FluoleadTM reacts with alkyl and aryl ketones, aldehydes and keto esters producing the corresponding difluoro products in high yields.^{2,6} Umemoto and co-workers² found that the deoxofluorination of cyclohexanone with FluoleadTM 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-FluorTM, which gives 2.6:1 and 1.5:1 mixtures in 79% and 94% yield.^{4a} FluoleadTM efficiently fluorinates diketones and non-enolizable ketones under very mild conditions, while fluorination of such substrates with SF₄, DAST and Deoxo-FluorTM requires severe conditions or give products in low yields.^{4b,c}

(B) Xu and co-workers developed a method to generate FluoleadTM in situ for the deoxofluorination of aldehydes and ketones.⁵ This method gives the *gem*-difluorinated products in good yields while problems associated with preparation and use of FluoleadTM are minimized and scrupulously dry reagents are not required.

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(C) It has been reported that Fluolead™ can react with carboxylic acids to give directly the corresponding trifluorinated product in good yield,⁶ a reaction that was only carried out with MoF₆^{7a} or SF₄,^{7b} 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.² When the replacement is carried out with DAST^{8a} or Deoxo-Fluor™,^{8b} 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.⁹

(F) 4-Fluoropyrrolidine derivatives are useful intermediates in the synthesis of bioactive compounds, such as dipeptidyl peptidase IV inhibitors.^{10a} The conventional method for preparing these derivatives from N-protected 4-hydroxyproline requires at least four steps.¹⁰ Recently, Singh and co-workers described a new methodology in two steps, using (2*S*,4*S*)-4-fluoropyrrolidine-2-carbonyl fluorides as synthons, which can be synthesized in high yields by stereospecific double fluorination of optically active N-protected (2*S*,4*R*)-4-hydroxyproline with Fluolead™.¹¹ 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 (2*S*)-2-(fluoromethyl)-*N*-tosylpyrrolidine from (2*S*)-*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.¹² The reaction with Fluolead™ was found to be much more selective and efficient than most reactions described in the literature using DAST^{13a} and Deoxo-Fluor™.¹³

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