SYNLETT
Spotlight 386

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

Fluolead

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Amanda Silva de Miranda was born in Divinópolis, Minas Gerais, Brazil, in 1986. She received her B.Sc. in Pharmacy (2008) from the Universidade Federal de Ouro Preto (UFOP) and her M.Sc. in Chemistry (2011) from the Universidade Federal of Rio de Janeiro (UFRJ), where she is currently working under supervision of Professor Eliezer J. Barreiro. Her research interest is focused on the synthesis of bioactive compounds, especially non-steroidal anti-inflammatory drugs.

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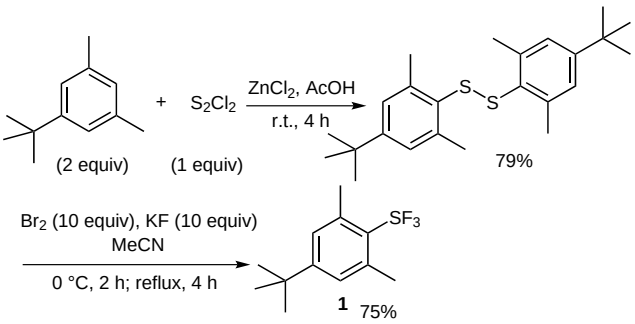
Introduction

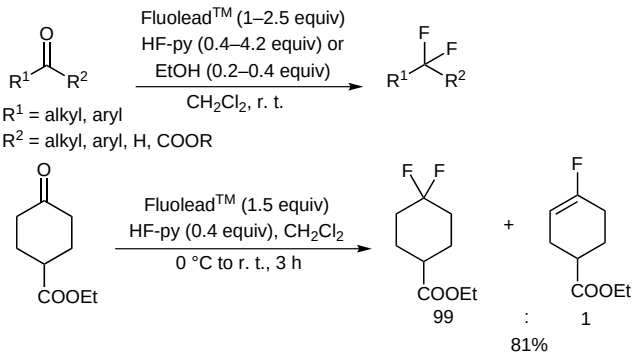
Fluorination is a very useful strategy in the design and synthesis of bioactive compounds, since the special nature of fluorine can confer enhanced binding interactions, metabolic stability and desirable physical properties to a molecule. In fact, approximately 5–15% of the total number of drugs launched 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 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]



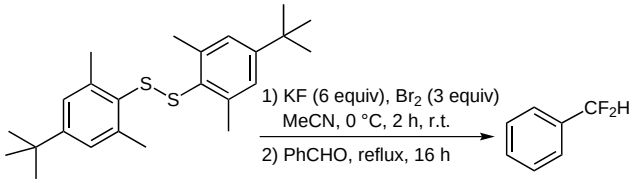
Scheme 1

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.[2,6] Umemoto and co-workers[2] 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.[4a] Fluolead™ efficiently fluorinates diketones and non-enolizable ketones under very mild conditions, while fluorination of such substrates with SF_4, DAST and Deoxo-Fluor™ requires severe conditions or give products in low yields.[4b,c]



(B) Xu and co-workers developed a method to generate Fluolead™ 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 Fluolead™ are minimized and scrupulously dry reagents are not required.



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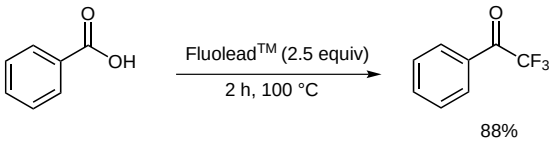
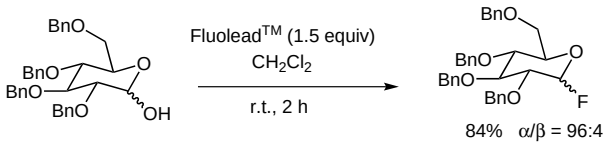
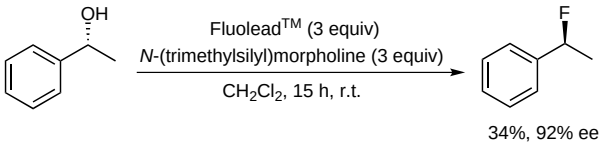
(C) It has been reported that Fluolead™ can react with carboxylic acids to give directly the corresponding trifluorinated product in good yield,[6] a reaction that was only carried out with MoF_6[7a] or SF_4,[7b] an extremely toxic gas.



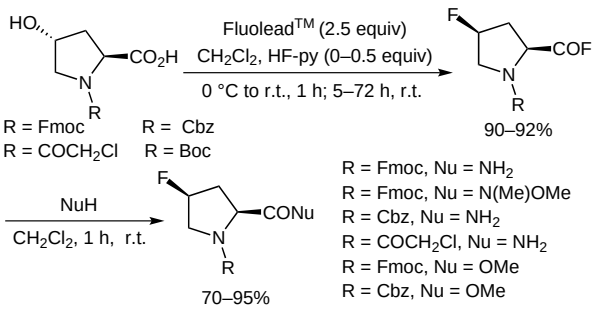
(D) A highly stereoselective deoxofluorination of D-glucopyranose with Fluolead™ giving 96:4 mixtures of α- and β-fluoro products was reported.[2] When the replacement is carried out with DAST[8a] or Deoxo-Fluor™,[8b] 11:89 and 28:72 mixtures of α- and β-isomers are obtained.



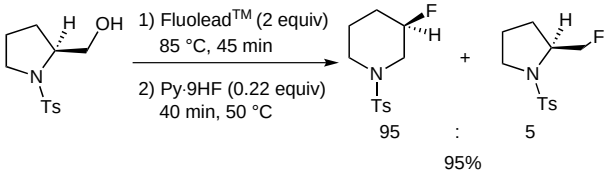
(E) Stereoselective deoxofluorination of enantiopure alcohols is difficult to achieve, particularly if the alcohol is prone to S_N1 reactions as in the case of benzylic alcohols. It has been reported that reaction of benzylic alcohol with Fluolead™ occurs with high stereochemical inversion and lead to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