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Oleg M. Michurin[a,b], Dmytro S. Radchenko[a,b,*], Igor V. Komarov[a,b]

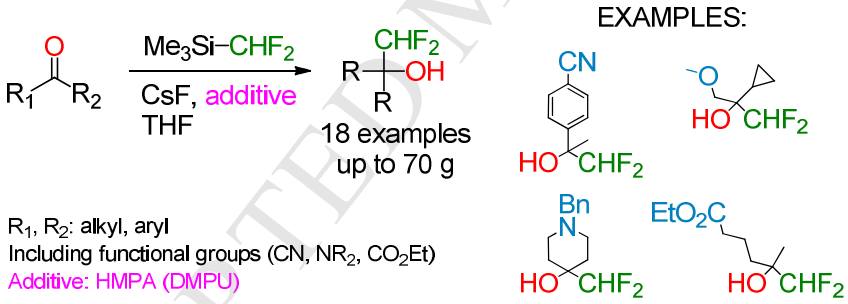
[a] Institute of High Technologies, Taras Shevchenko National University of Kyiv, Volodymyrska 60, 01601 Kyiv, Ukraine, Tel: +38 097 9931939; Fax: +38 044 5373253

[b]Enamine Ltd., Matrosova 23, 01103 Kyiv, Ukraine

E-mail: dmitry.radchenko@mail.google.com, dmitry.radchenko@mail.enamine.net

Abstract

Easily available difluoromethylating reagent Me_3SiCF_2H enables multigram synthesis of difluoromethyl alcohols in good yields under mild conditions from a number of aldehydes and ketones in the presence of HMPA. This additive makes possible the previously challenging nucleophilic difluoromethylation of enolizable ketones. DMPU can be used as a non-toxic alternative to the HMPA in the difluoromethylation reaction, albeit the yields were slightly lower in this case. The method works well with cyclic, acyclic, aryl ketones and tolerates various functional groups.



Key words: addition, catalysis, fluorine, ketones, nucleophilic difluoromethylation.

Introduction

Incorporation of fluorine in organic molecules modulates their pharmacological properties and has become almost a standard practice in medicinal chemistry. The unique properties of fluorine such as high electronegativity, excellent NMR parameters, low abundance in biosphere, ability to mimic hydrogen and block metabolic processes, increased lipophilicity and bioavailability of fluoroorganic molecules has made fluorine the "second-favourite heteroatom" after the nitrogen in drug design.[1] It is estimated that 30–40% of agrochemicals and 20% of pharmaceuticals contain fluorine.[2] The difluoromethyl group (CF_2H) has a great potential in the design of pharmaceuticals, agrochemicals, and materials. In the area of medicinal chemistry, the CF_2H groups prove to be a useful bioisostere of a hydroxy group, mainly because it is a lypophilic hydrogen bond donor, offering a potential for