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Catalytic trifluoromethylation of aldehyde and potential application for pyrano[4,3-b]quionline synthesis

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ABSTRACT

We have described CsF-catalyzed trifluoromethylation of heteroaromatic aldehydes at room temperature to afford trifluoromethyl group containing alcohols in very good yields. Using catalytic amount of CsF (0.2 eq.) in toluene, trifluoromethylated product were achieved in good yields at rt. The substrate scope has been exemplified by a large number of substrates. As an application, iodo etherification/cyclization has also been demonstrated for the synthesis of trifluoromethyl pyrano[4,3-b]quinoline from o-alkynyltrifluoro methyl alcohol, in very good yield.

Introduction

The incorporation of trifluoromethyl (CF_3) group into organic molecules leads to profound changes in their physical and chemical properties, metabolic stability and lipophilicity.[1] Trifluoromethyl-containing molecules are frequently used in drug design and agrochemicals because of significant enhancement in their bioactivities as compared to their methyl analogues.[2] Figure 1 shows selected examples of biologically and pharmaceutically potent molecules, which contain trifluoromethyl group. Compound **a** is used for antiinflammatory effects in cancer treatment,[3] **b** shows inhibition of cholesteryl ester transfer protein relevant to heart disease[4] and **c** shows sleep induction.[5] Similarly, quinoline and its derivatives have always attracted great attention to both synthetic and biological chemist because of their various pharmacological properties.[6] There are number of natural products of quinoline skeleton with an alcohol group which have been used as medicine or have been employed as lead molecule for the development of newer and potent drugs.[7] For example, quinine **d** was isolated from the bark of Cinchona trees and has been used for the treatment of malaria. Its structure determination and SAR studies resulted in discovery of newer antimalarial drugs mefloquine **e**, having CF_3 group. Thus owing to the great changes in chemical and biological properties of quionline molecules after the introduction of trifluoromethyl group, considerable efforts have been devoted for introducing CF_3 group into quinoline skeleton.[8]

Trifluoromethylation of carbonyl compounds is one of the most straightforward methods for introducing CF_3 group into organic molecules. Ruppert-Prakash reagent (Me_3SiCF_3) has been widely used as nucleophilic reagent for the transformation of carbonyl group to trifluoromethyl substituted alcohol. Other reagents such as sodium trifluoroacetate[9a], alkyl trifluoromethanesulfinates[9b] and phenyl trifluoromethylsulfone reagents[9c] were recently used in the synthesis of trifluoromethyl group containing alcohol. However, these reagents were not examined with heteroaromatic aldehydes.

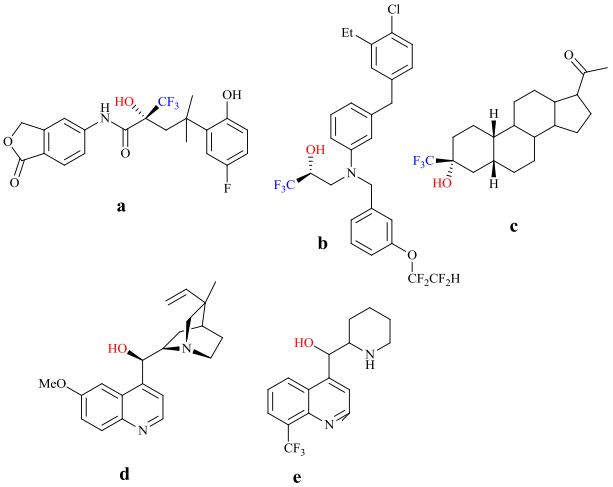

Fig. 1: Drug molecules with trifluoromethyl group

We have been involved for several years in exploring the synthetic applications of 2-chloroquinoline-3-carboxaldehydes and 3-carbonitriles analogues for the synthesis of various quionline derived frameworks.[10] Recently, we have reported

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