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Abstract

The first representatives of a previously unknown class of highly reactive functionalized pyrrole compounds, 3-(pyrrol-2-yl)propiolaldehydes, have been synthesized by the transition metal-free, mechanoactivated ethynylation of pyrroles with 3-iodopropiolaldehyde using a solid K_2CO_3 medium under mild conditions (room temperature, 4 h) in yields of up to 58%.

Keywords

3-(pyrrol-2-yl)propiolaldehydes; bromopropiolaldehyde; iodopropiolaldehyde; ethynylation

Introduction

Among the great diversity of functionalized pyrroles, pyrrolylpropiolaldehydes have until now remained unknown despite their obvious synthetic potential. Indeed, the pyrrole core is itself abundant in various essential natural products including chlorophyll, bile pigments, heme, and vitamin B_{12}.[1] The pyrrole ring also forms the structural unit of various compounds possessing anticancer,[2-5] cytotoxic, anti-tubercular, antimicrobial, anti-inflammatory, antioxidant, antimalarial, enzyme inhibitory, hypolipodemic,[4,5] and anti-HIV activities.[6]

In turn, acetylenic aldehydes, particularly propiolaldehydes, have proved to be highly attractive synthetic motifs. The triple bond conjugated with an aldehyde functional group thus represent powerful synthons in organic chemistry.[7-11] Based on propiolaldehydes, a variety of pharmaceutically-oriented heterocycles have been obtained, including antitumor anthrapyran antibiotics,[12] a potent anticancer natural product FR901464 that lowers the mRNA levels of oncogenes and tumor suppressor genes,[13] and macrolactin A.[14] Further examples regarding the application of propiolaldehydes for the preparation of diverse compounds with valuable biological activities include phyllamycins A and C, justicidin B, retrojusticidin B,[15] 70-desmethylkealiiquinone, an analogue of the marine alkaloid kealiiquinone,[16] japonilure,[17] 3,5-disubstituted 6*H*-pyrrolo[1,2-*c*][1,2,3]triazoles,[18] and 1,4-dihydroquinolines.[19]

The conjugation of the propiolaldehyde and pyrrole moieties in one molecule may synergistically strengthen the potential of such compounds as synthetically and medicinally important targets. The lack of information regarding pyrrole acetylenecarbaldehydes is due to the absence of suitable methods for their synthesis. Even common and efficient protocols for the introduction of ethynyl substituents to arene or heteroarene rings, such as the Sonogashira coupling reaction, appear to be insufficient in the case of alkynes with electron-withdrawing functional groups.[20]

Results and discussion

Herein, we report the first method for the synthesis of 3-(pyrrol-2-yl)propiolaldehydes *via* the cross-coupling of pyrroles **1a-j**, **4** with bromo- and iodopropyolaldehydes in solid K_2CO_3, thus