New 1,3,4-Oxadiazolyl-pyrazolyl-Pyridine Tricyclic Scaffold Derivatives: Synthesis and Structure Assignment by NMR and DFT Calculations

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INTRODUCTION

Among five-membered aromatic heterocycles, 1,3,4-oxadiazoles are important class of aromatic heterocycles displaying a broad spectrum of biological activities, such as antimicrobial, anti-inflammatoy, analgesic, anticonvulsivant, anti-hypoglycemic.[1] Compounds containing oxadiazole moieties have been described as possessing anticancer or muscle relaxant activity and have been used as fluorescent whiteners.[2] Usually, the synthesis of non-symmetrical 2,5-disubstituted 1,3,4-oxadiazoles has mainly been done by dehydratation of diacylhydrazines or oxidative cyclization of aldehyde *N*-acylhydrazones, but many other reagents and reaction conditions have been reported to achieve their obtainment.[3]

RESULTS AND DISCUSSION

Following our previous work[4] and in attempting to introduce another class of nitrogenated azoles into the pyrazolyl-pyridine system, compounds methyl 6-[alkyl/aryl-5-trifluoro-methyl-1*H*-pyrazol-1-yl]nicotinate hydrochloride **1a-b** were reacted firstly with hydrazine hydrate under reflux of ethanol to give the hydrazides of **2a-b**. These hydrazides were submitted to a cyclocondensation reaction with $R^1C(OEt)_3$ (**3**), where R^1 = methyl (**3a**) and phenyl (**3b**), leading to the obtention of four examples of oxadiazolyl-pyrazolyl-pyridines (**4aa-bb**),at moderate yields (Scheme 1). As the reaction property, the orthoesters were used simultaneously as solvent and reagent and compounds of **4aa-bb** precipitated steadily during the reaction time at 110 ºC. Compounds **4aa-bb** were characterized by ^{1}H and ^{13}C NMR spectroscopy and thus, in order to assign the conformation of the oxadiazolyl-pyrazolyl-pyridines (**4**) we employed theoretical calculations using the Density Functional Theory (DFT) method.[5]

CONCLUSION

To demonstrate the applicability of the esters **1**, new hydrazides **2** and their oxadiazolyl-pyrazolyl-pyridines **4** were able to be produced as a new triheterocyclic scaffold at moderate yields.

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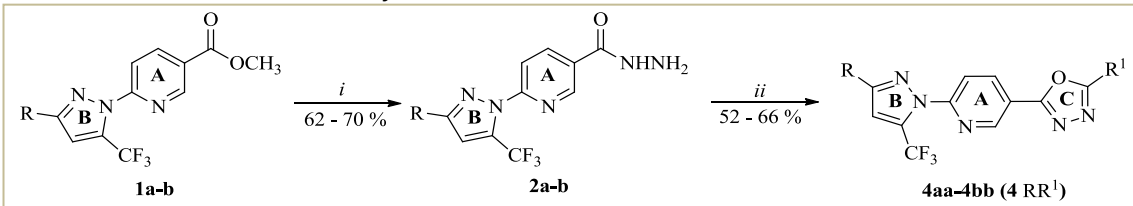

Scheme 1. Reagentes and conditions: (*i*) $NH_2NH_2.H_2O$, EtOH, reflux, 20 h; (*ii*) (**3**) $R^1C(OEt)_3$, 110 °C, 16 h. R = Me, Ph; R^1 = Me, Ph.