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An easy synthesis of 5-functionally substituted ethyl 4-amino-1-aryl- pyrazolo-3-carboxylates: interesting precursors to sildenafil analogues

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Abstract

3-Oxo-2-arylhydrazononitriles **1a-c** react readily with chloroacetonitrile, ethyl chloroacetate, and with phenacyl chloride to give 4-aminopyrazoles **4a-e**. The pyrazolo[4,3-*d*]pyrimidine derivatives **7** and **10** are synthesized via reaction of the aminopyrazole **4b** with phenylisothiocyanate and DMFDMA/NH_4OAc respectively.

Background

Interest in the chemistry of 4-aminopyrazole carboxylic acid derivatives has recently been recognized as their derivatives are ideal precursors for the synthesis of biologically active pyrazolo[4,3-*d*]pyrimidine ring systems [1-6]. The reported synthetic approaches to these derivatives are also multistep, non atom economical and non eco friendly [1,5,6]. Recently however a route to 4-aminopyrazole-5-carboxylic acid derivatives via reacting 2-arylhydrazononitriles with α-haloacid derivatives has been reported by Elnagdi et al [7,8] as well as other researchers [9]. In the present article we report results of our work aimed at exploring this synthetic methodology and adoption of products for the synthesis of pyrazolo[4.3-*d*]pyrimidines.

Thus, compounds **1a-c**, were prepared according to literature procedures via coupling of ethyl cyanoacetate with aromatic diazonium salts [10]. It has been found that **1a-c** react with α-chloroacetonitrile **2a** to yield **4a-c**, most likely via acyclic intermediates **3a-c** that could not be isolated. The structure of **4a-c** was confirmed based on ^{1}H NMR spectra that revealed the presence of amino signals and also ^{13}C NMR which revealed the presence of only one CN signal. Similarly reacting **1b** with ethyl chloroacetate **2b** and with phenacyl chloride **2c** afforded **4d,e**. The structure of **4d,e** was also confirmed based on IR and ^{13}C NMR, which revealed the absence of CN bands and signals (cf. Scheme 1).