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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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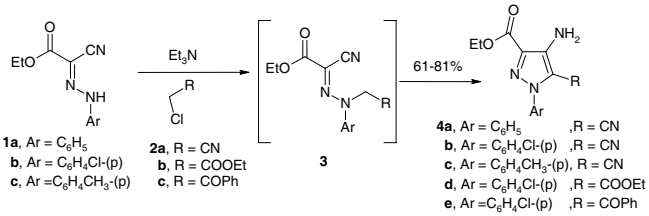
## Abstract

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.

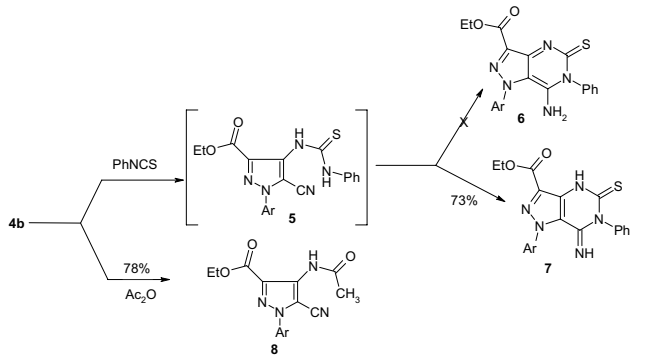
## Background

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 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 $^1H$ 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).



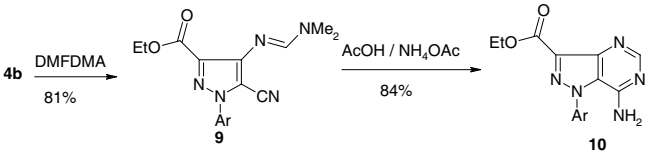

**Scheme 1: synthesis of Ethyl 4-amino-5-substituted-1-aryl-1*H*-pyrazole-3-carboxylates (4)**

Compound **4b** reacted readily with phenylisothiocyanate to yield a 1:1 adduct. The IR and $^{13}C$ NMR spectra of the product revealed the absence of CN bands and signals. Thus structure **6** or **7** is suggested. $^1H$ NMR showed two NH signals at δ 8.33 and 10.3 ppm, thus structure **7** is assigned for the reaction product. Acetylation of **4b** in acetic anhydride afforded monoacetyl derivative **8**. (cf. Scheme 2)



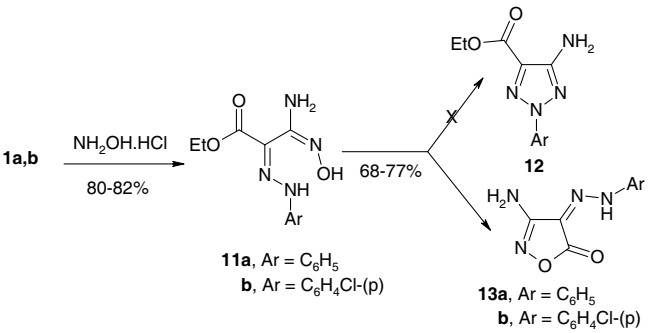

**Scheme 2: Reactivity of pyrazole 4b with phenylisothiocyanate and acetic anhydride**

Compound **4b** condensed with dimethylformamide dimethylacetal (DMFDMA) to yield the enamine **9**. The $^1$H NMR spectrum indicated two distinct singlets at ä 2.97 and 3.05 ppm for the *N*,*N*-dimethylamino protons which mean that the two methyl groups are magnetically non-equivalent, as to be expected. Compound **9** could be readily converted into pyrazolo[4,3-*d*]pyrimidine **10** on treatment with AcOH/$NH_4$OAc mixture. (cf. Scheme 3)




**Scheme 3: Conversion of pyrazole 4b Ethyl into pyrazolo[4,3-*d*]pyrimidine-3-carboxylate 10**

Compound **1** reacted with hydroxylamine hydrochloride in ethanol/sodium acetate solution to yield amidooxime **11** as in the literature [10]. Trials to cyclize the amidooxime into 1,2,3-triazole **12** utilizing the reaction conditions described earlier in literature [11] failed. However, the amidooxime **11** cyclizes smoothly via loss of ethanol in DMF and in presence of anhydrous sodium acetate into isoxazolone **13**. (cf. Scheme 4)




**Scheme 4: Conversion of arylhydrazononitriles 1 into 3-Amino-4-arylhydrazono-4*H*-isoxazol-5-one**

## Conclusion

We could show that arylhydrazononitriles **1a-c** are valuable precursors to 4-amino-5-substituted-1-aryl-1H-pyrazole-3-carboxylic acid ethyl ester which can be used for preparation of sildenafil analogues.

### *Experimental*

See additional file no. 1 for full experimental data

## Additional material

### Additional file 1

*The experimental section. The experimental data and the results of analysis*

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