SYNTHESIS AND CHARACTERIZATION OF NEW POLYCYCLIC NITROGEN HETEROCYCLE COMPOUNDS VIA MULTICOMPONENT REACTIONS FROM 3-ALKOXY-1*H*-PYRAZOLE-4-CARBALDEHYDES

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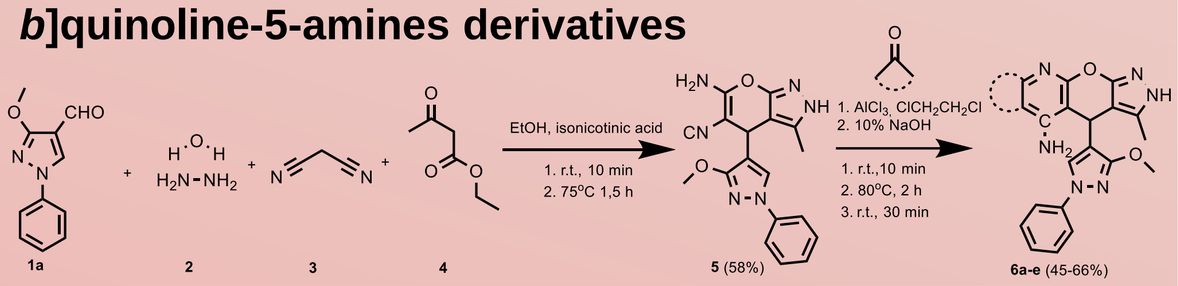
Introduction

Multicomponent Reactions (MCRs) in which three or more starting materials react to form a product, where basically all or most of the atoms contribute to the newly formed derivative, are considered to be an important methodological arsenal in synthetic and medicinal chemistry [1]. These reactions have been strategically employed in various synthetic transformations where classical methods usually involve many steps with difficult procedures. MCRs exhibit advantages such as atom economy and waste prevention, because of the reduced number of work-up, extraction and purification procedures [2]. Therefore MCRs are often considered as useful alternative to sequential multistep synthesis.

Pyrazole ring containing compounds are considered pharmacologically important because of many biological activities such as antioxidant, antibacterial, anticancer, anti-inflammatory and more [3,4]. This heterocyclic moiety can be found in structure of many well-known drugs for different therapeutic treatments.

Synthesis of 2*H*-pyrazolo[4',3':5,6]pyrano[2,3-*b*]quinoline-5-amines derivatives



1a **2** **3** **4** **5** (58%) **6a-e** (45-66%)

Ketones	Yield (%)	Ketones	Yield (%)
a cyclohexanone	66	**d** 4-phenylcyclohexan-1-one	64
b 4-methylcyclohexan-1-one	52	**e** 4-propylcyclohexan-1-one	45
c 4,4-dimethylcyclohexan-1-one	50		

Fig 1. Synthesis of 2*H*-pyrazolo[4',3':5,6]pyrano[2,3-*b*]quinoline-5-amines derivatives

For the synthesis of compounds **6a-e** a two-step reaction sequence was applied (Fig. 1). A four-component MCR reaction between the 3-methoxy-1-phenyl-1*H*-pyrazole-4-carbaldehyde, hydrazine hydrate, ethyl acetoacetate and malononitrile in presence of isonicotinic acid as a catalyst resulted in a formation of pyrano[2-3-*c*]pyrazole **5**.

In the next step, $AlCl_3$ catalyzed reaction was performed between the obtained pyrano[2,3-*c*]pyrazole **5** and cyclic ketones which resulted in the formation of products **6a-e** in good yield.

Conclusion

In conclusion we have demonstrated that 3-alkoxy-1*H*-pyrazole-4-carbaldehydes can be successfully used as starting materials in convenient and practical multi-component reactions. A pyrazolyl-substituted 2,4-dihydropyrano[2,3-*c*]pyrazole was synthesized via one-pot four-component reaction of ethyl acetoacetate, hydrazine hydrate, malononitrile and pyrazole-4-carbaldehyde and further subjected to $AlCl_3$ catalyzed Friedländer reaction with cyclic ketones. Hantzsch reaction was used for the preparation of pyrazole-dihydropyridine derivatives by condensation of pyrazole-4-carbaldehydes with ethyl acetoacetate in the presence of ammonium acetate. The reaction products were further oxidised and novel pyrazole-pyridine derivatives were obtained. The structures of the synthesized compounds were confirmed by ^{1}H, ^{13}C and ^{15}N NMR spectroscopy.

References

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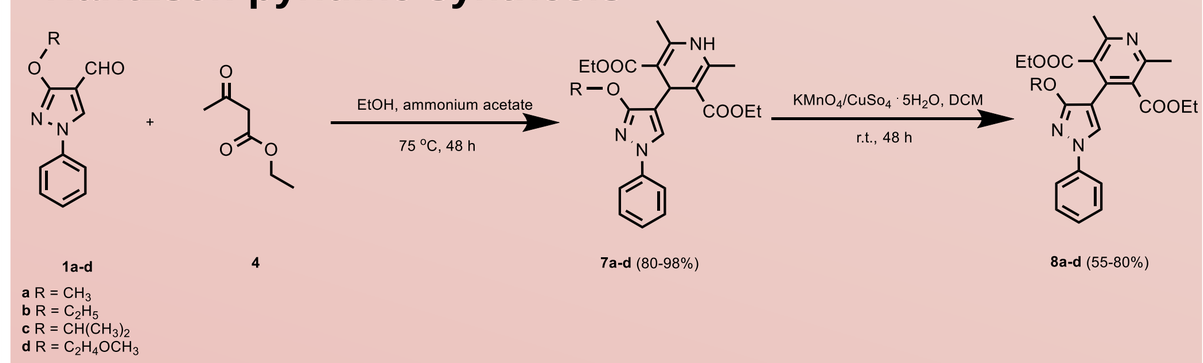
Hantzsch pyridine synthesis



1a-d **4** **7a-d** (80-98%) **8a-d** (55-80%)

a R = CH_3
b R = C_2H_5
c R = $CH(CH_3)_2$
d R = $C_2H_4OCH_3$

Fig 2. Synthesis pathway for novel pyrazole-piridine derivatives

1,4-Dihidropyridines **7a-d** were obtained in good yields using multicomponent Hantzsch pyridine synthesis reaction between various 3-alkoxy-1*H*-pyrazole-4-carbaldehydes **1a-d**, ethyl acetoacetate **2** and a nitrogen donor - ammonium acetate refluxing reaction mixture in EtOH.

The dihydropyridine ring was further oxidised by $KMnO_4/CuSO_4$, which was prepared by simply grinding equal weights of $KMnO_4$ and $CuSO_4$ until homogeneous powder. To a mixture of appropriate 1,4-dihydropyridine **7a-d** solution in DCM an oxidant was added and pyridines **8a-d** were obtained in good yields.

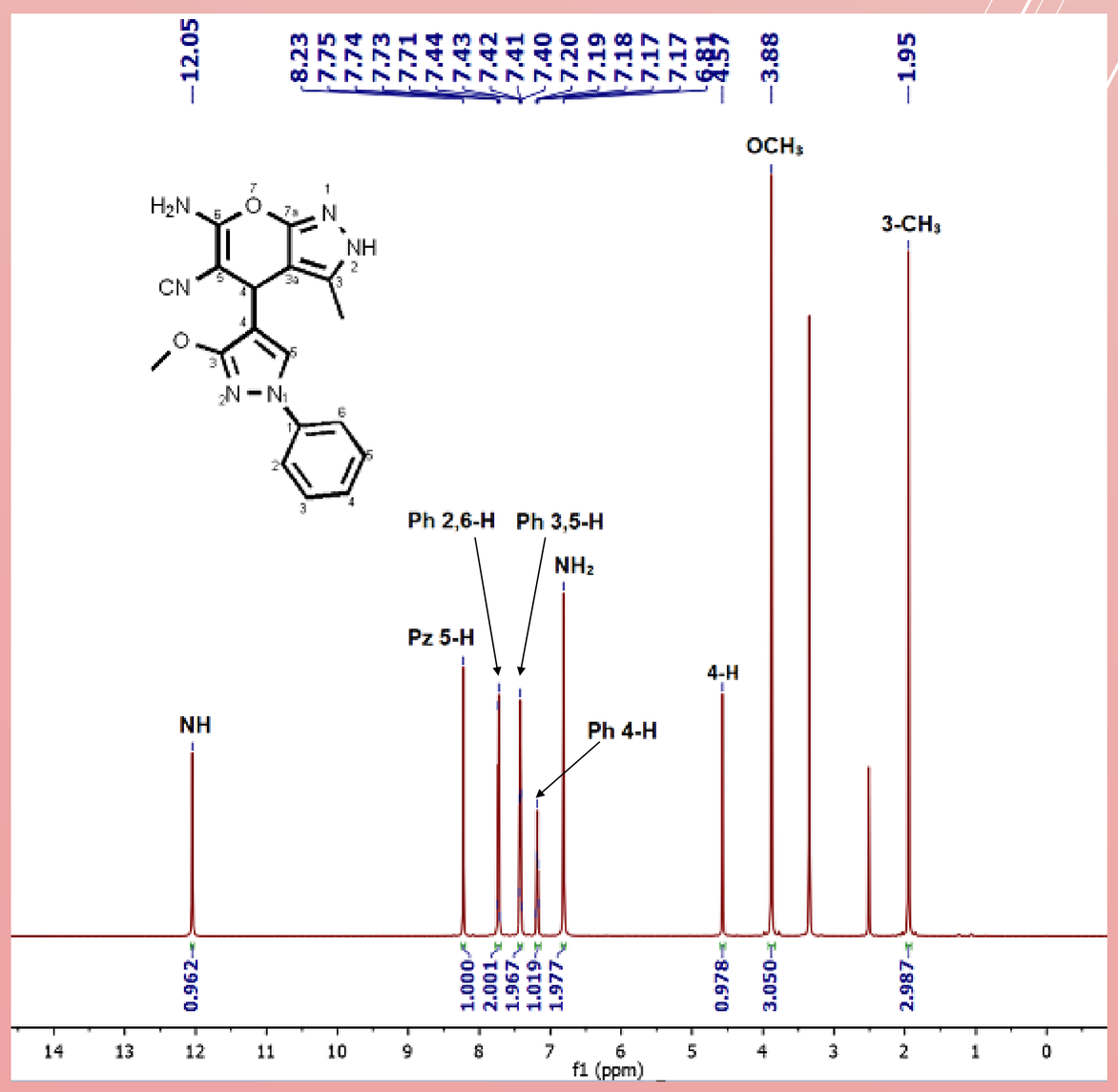


Fig 3. ^{1}H NMR spectrum of compound **5** (DMSO-d_6)