Synthesis of new 4,7-dihydropyrazolo[1,5-a]pyrimidines and 4,5,6,7,8,9-hexahydropyrazolo[5,1-b]quinazolines through the non-catalyzed Biginelli reaction

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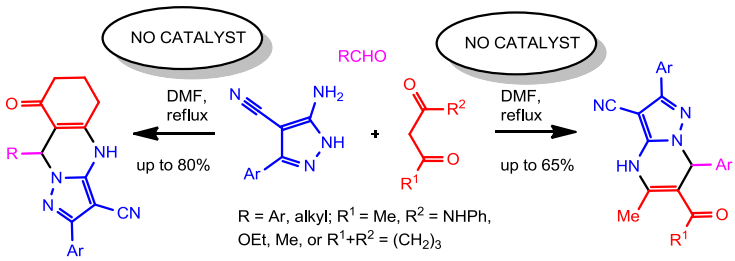
Abstract: The Biginelli-type reactions of 5-amino-3-arylpyrazole-4-carbonitriles with aldehydes and 1,3-dicarbonyl compounds were studied in details. New pyrazolopyrimidines and pyrazoloquinazolines were synthesized through the reaction of 5-amino-3-arylpyrazole-4-carbonitriles with aromatic aldehydes and active 1,3-dicarbonyls (acetyl acetone, acetoacetanilides or cyclohexanedione) in the boiling DMF. The reaction requires no catalysts.

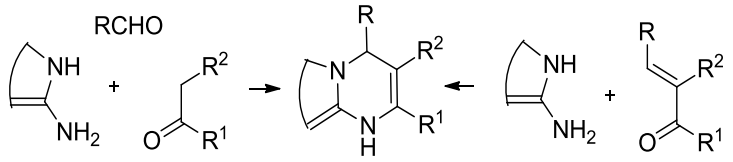
Keywords: Biginelli reaction, uncatalyzed reactions, pyrazolo[1,5-a]pyrimidines, pyrazolo[5,1-b]quinazolines



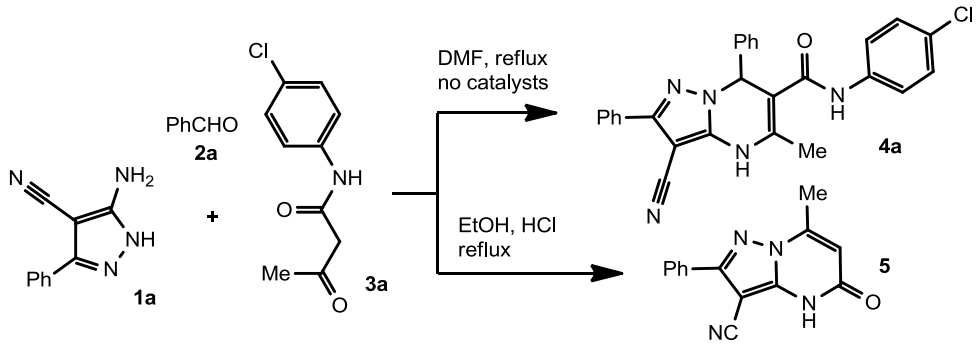
In last two decades, the classical urea-based multicomponent reaction named after Italian chemist Pietro Biginelli, as well as the reactions of so-called Biginelli compounds (3,4-dihydropyrimidin-2(1H)-ones and -thiones) have attracted great attention [1-9]. Less attention is paid to the non-classical Biginelli-type reaction employing aminoazoles as N,N-dinucleophilic components. Our interests have been focused on the chemistry of unusual Biginelli-type compounds and, particularly, on the chemistry of pyrazolo- and triazolo[1,5-a]pyrimidines. Pyrazolo[1,5-a]pyrimidines are important scaffolds which are present in many synthetic drugs such as dorsomorphin or other bone morphogenetic protein receptor inhibitors useful for treatment of anemia, muscular dystrophy, atherosclerosis etc. Pyrazolo[1,5-a]pyrimidines also have been recognized as purine analogs with c-AMP phosphodiesterase inhibitory activity, tyrosine kinase inhibitors.

Two most commonly used approaches to build 4,7-dihydroazolo[1,5-a]pyrimidine core are known. The first one consists of the reaction of 3(5)-aminoazoles with α,β-unsaturated carbonyls (for reviews see [10-12]) and the other

is based on the modified Biginelli reaction of 3(5)-aminoazoles with aldehydes and active methylene carbonyl compounds [9-12] (Scheme 1).



Easily available 5-aminopyrazole-4-carbonitriles could be considered as perspective reagents bearing reactive cyano group at C-4, which may react under Biginelli conditions to afford functionalized heterocycles. We have studied the reaction of 5-amino-3-arylpyrazole-4-carbonitriles with active methylene 1,3-dicarbonyls and aldehydes with the aim to develop a synthetic route toward DPPMs. As a model reaction, we examined the reaction of 5-amino-3-phenylpyrazole-4-carbonitriles **1a** with benzaldehyde **2a** and N-(4-chlorophenyl)-3-oxobutanamide **3a** (Scheme 2) in boiling DMF with no catalysts. As expected, the reaction proceeds smoothly to give DPPM **4a**. In order to optimize the reaction conditions, we studied the effect of solvent amount, reaction time, reagents ratio and different work-up procedures on the yields of the target product **4a**.



The best yield of pure **4a** (60% after recrystallization) was obtained when the reagents were taken in equimolar amounts and the reaction was conducted in a three-component mode. The best results were obtained when minimum amount of DMF (0.5 mL per ~2 mmol of each reagent) were used, under short term heating (~ 20 min) and with a final precipitation of the product by addition of MeOH. Meanwhile, the reaction **1a+2a+3a** in boiling EtOH under acid catalyzed conditions (HCl) proceeds in a quite different way to give pyrazolo[1,5-a]pyrimidine-5(4H)-one-3-carbonitrile **5** in 35% yield. According to the NMR data for crude pyrazolopyrimidine **4a**, product **5** is also the main by-product of the uncatalyzed process. With the optimized procedure in hands, we have obtained the analogs of compound **4a** in 32-53% yields (Table 1). However, we failed to obtain DPPMs **4** by ternary condensation of aminopyrazole **1b** with aldehydes and 2,4-pentanedione. Instead, the sole isolated product was 5,7-dimethylpyrazolo[1,5-a]pyrimidine-3-carbonitrile **6** as the result of the reaction of 1b with 2,4-pentanedione alone (Scheme 3). Noteworthy that the reaction proceeds notwithstanding the conditions of temperature or acidity of reaction media.

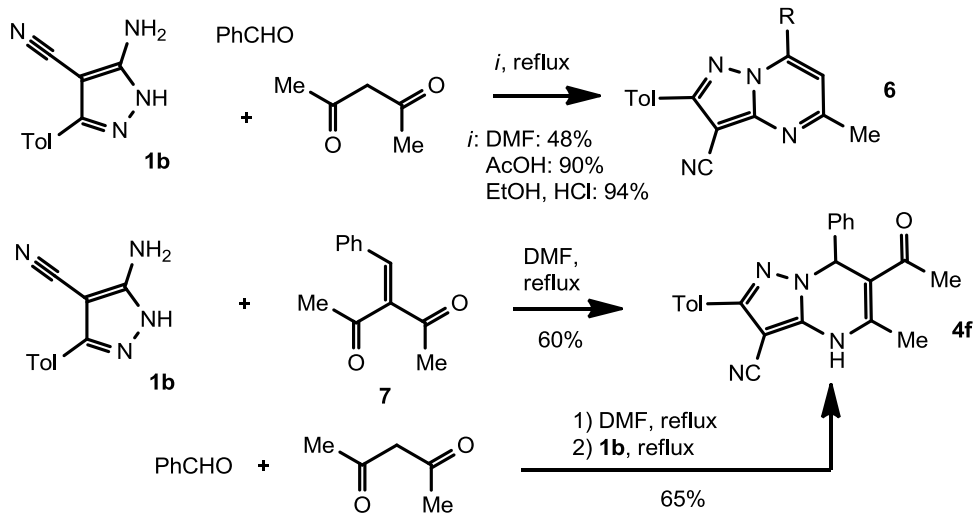


Table 1. Synthesis of DPPMs **4b-g**

Entry	Product	Ar	R	R^1	Yield (%)[a]
1	**4b**	4-MeC_6H_4	Ph	4-ClC_6H_4NH	37
2	**4c**	Ph	4-$NO_2C_6H_4$	4-ClC_6H_4NH	52
3	**4d**	4-MeC_6H_4	4-$NMe_2C_6H_4$	4-ClC_6H_4NH	32
4	**4e**	4-MeC_6H_4	Ph	OEt	53

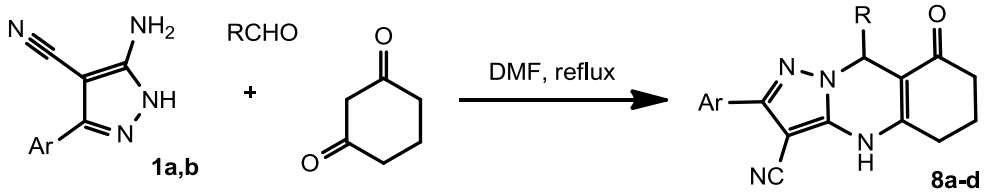
The yields are given for pure products after recrystallization from MeOH.

Unsaturated diketone **7** reacts with aminopyrazole **1b** to afford the desired DPPM **4f** in a good yield. In order to find optimal conditions, we attempted to combine the preparation of starting endione **7** and Biginelli-type condensation in a one-pot procedure. Thus, when PhCHO and acetylacetone were briefly heated in DMF to give condensation product **7** followed by treatment with aminopyrazole **1b**, the compound **4f** was obtained in 65% yield. Using the same approach, ethyl acetoacetate was converted into 4,7-dihydropyrazolo[1,5-a]pyrimidine **4e** in 53% yield. It should be noted that, despite the known benefits of base-catalyzed Biginelli-type reactions or non-catalyzed protocols, most methods commonly used for the synthesis of Biginelli compounds require an acid as a catalyst.

We have to admit that the above Biginelli-type reaction may proceed without any additional catalysts, at least at certain cases. In the present case, an acid catalyst strongly disfavors formation of the desired Biginelli products. Nevertheless, HCl was found to be a good catalyst for the reaction between aminopyrazoles **1a** and 1,3-dicarbonyls.

The obtained results encouraged us to continue our studies with other dicarbonyl compounds. Thus, 1,3-cyclohexanedione reacts with aminopyrazoles **1a,b** and

aldehydes to give the expected 2-aryl-8-oxo-4,5,6,7,8,9-hexahydropyrazolo[5,1-b]quinazolin-3-carbonitriles **8a-d** in 47-80% yields.



In conclusion, we have developed simple and selective synthetic protocol based on the Biginelli-type multicomponent reaction of 5-amino-3-arylpyrazole-4-carbonitriles with aldehydes and 1,3-dicarbonyl compounds. The reported method provides catalyst-free access to functionalized 4,7-dihydropyrazolo[1,5-a]pyrimidine-3-carbonitriles and 4,5,6,7,8,9-hexahydropyrazolo[5,1-b]quinazolin-3-carbonitriles.

General process for preparation of pyrazolopyrimidines 4a-g and pyrazoloquinazolines 8a-d.

The mixture of appropriate aldehyde (2.2 mmol), 1,3-dicarbonyl compound (2 mmol) and the corresponding aminopyrazole **1** (2 mmol) in DMF (0.5 mL) was heated under reflux for 20 min. The mixture was cooled and MeOH (20 mL) was added. The precipitate was filtered off and washed with MeOH (3 × 3 mL).

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