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Proceeding Paper

On the Acylation of 1,6-Diamino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles †

Alexandra R. Chikava [1], Alexei A. Dolganov [1] and Victor V. Dotsenko [1,2,3]*

[1] Kuban State University, 149 Stavropolskaya str, Krasnodar 350040, Russia; latypova9419@mail.ru (A.R.C.); alexsm2004@gmail.com (A.A.D.)
[2] ChemEx Lab, Vladimir Dal' Lugansk National University, 20A/7 Molodezhny, Lugansk 91034, Russia
[3] Department of Chemistry, North Caucasus Federal University, 1a Pushkin St., Stavropol 355009, Russia
* Correspondence: victor_dotsenko_@mail.ru
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Abstract: Here, 1,6-diamino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles, prepared by the reaction of cyanoacethydrazide with arylmethylene malononitriles, react with 1-cyanoacetyl-3,5-dimethylpyrazole and chloroacetyl chloride to give corresponding cyanoacetamides and chloroacetamides. The reaction with phthalic anhydride proceeds under harsh conditions to give 4,7-dioxo-4,7-dihydropyrido[1′,2′:2,3][1,2,4]triazolo[5,1-a]isoindole- 1,3-dicarbonitriles.

Keywords: cyanoacethydrazide; N-aminopyridines; cyanoacetylation; heterocyclization

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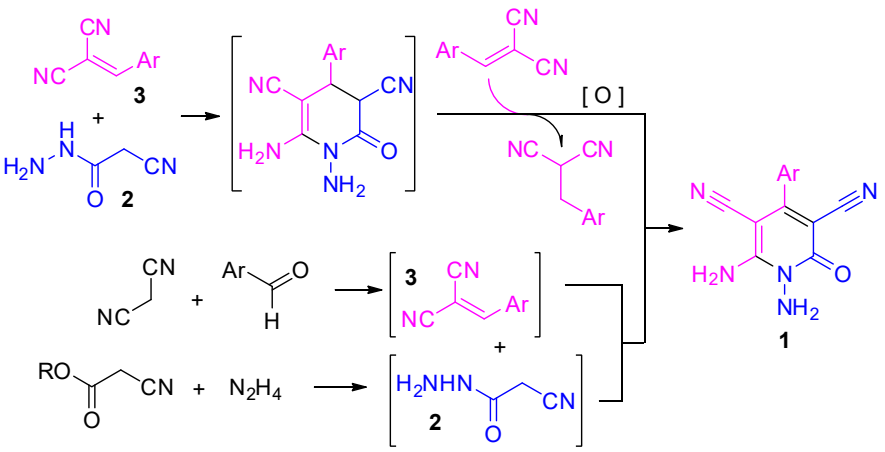
1. Introduction

In 1981, 1,6-Diamino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles **1** were first prepared by Soto and colleagues through the reaction of cyanoacethydrazide **2** with two eq. arylmethylene malononitriles **3** [1] (Scheme 1). The reaction also may be performed in a multicomponent mode, using corresponding aldehyde, malononitrile and cyanoacethydrazide **2**. The 1,6-diaminopyridines **1** are highly functionalized, promising reagents that can be used to build various nitrogen-bridged polyheterocyclic systems (for a review, see [2]). A survey of the literature revealed a lack of information on the reaction of 1,6-diamino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles **1** with functionalized acylating agents such as 1-cyanoacetyl-3,5-dimethylpyrazole, chloroacetyl chloride and phthalic anhydride. Consequently, we decided to fill this gap by performing the aforementioned reactions ourselves.

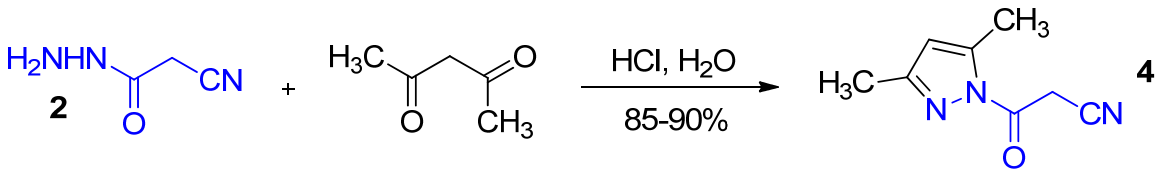


Scheme 1. The preparation of 1,6-diamino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles **1**.

2. Results and Discussion

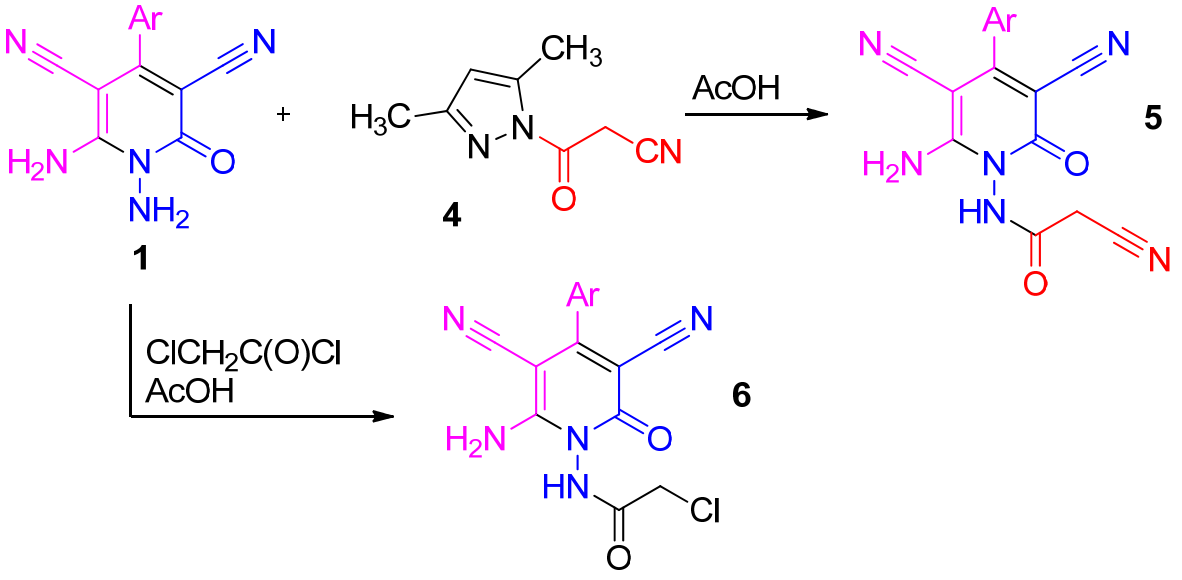
First, we prepared a series of the starting compounds **1**. We confirmed the observation of Soto and colleagues [1] that high yields of compounds **1** may be achieved only when arylmethylene malononitriles **3** are taken in at least two-fold excess with respect to cyanoacethydrazide **2**. Thus, the true oxidant in the reaction is arylmethylene malononitrile **3**, not atmospheric oxygen.

In 1957, 1-Cyanoacetyl-3,5-dimethylpyrazole **4** (3-(3,5-dimethyl-1H-pyrazol-1-yl)-3-oxopropanenitrile, cyanoacetylpyrazole) was introduced into synthetic practice by Ried and Meyer [3] and, since then, it has established itself as a highly effective cyanoacetylating agent—more powerful than ethyl cyanoacetate and less impractical, stabler and more convenient than cyanoacetyl chloride. As of 2020, the chemical properties of 1-cyanoacetyl-3,5-dimethylpyrazole **4** have been covered in several review papers [4–6]. It has been prepared by a reaction of cyanoacethydrazide **2** with acetylacetone in aqueous HCl by a reported procedure [7] (Scheme 2):



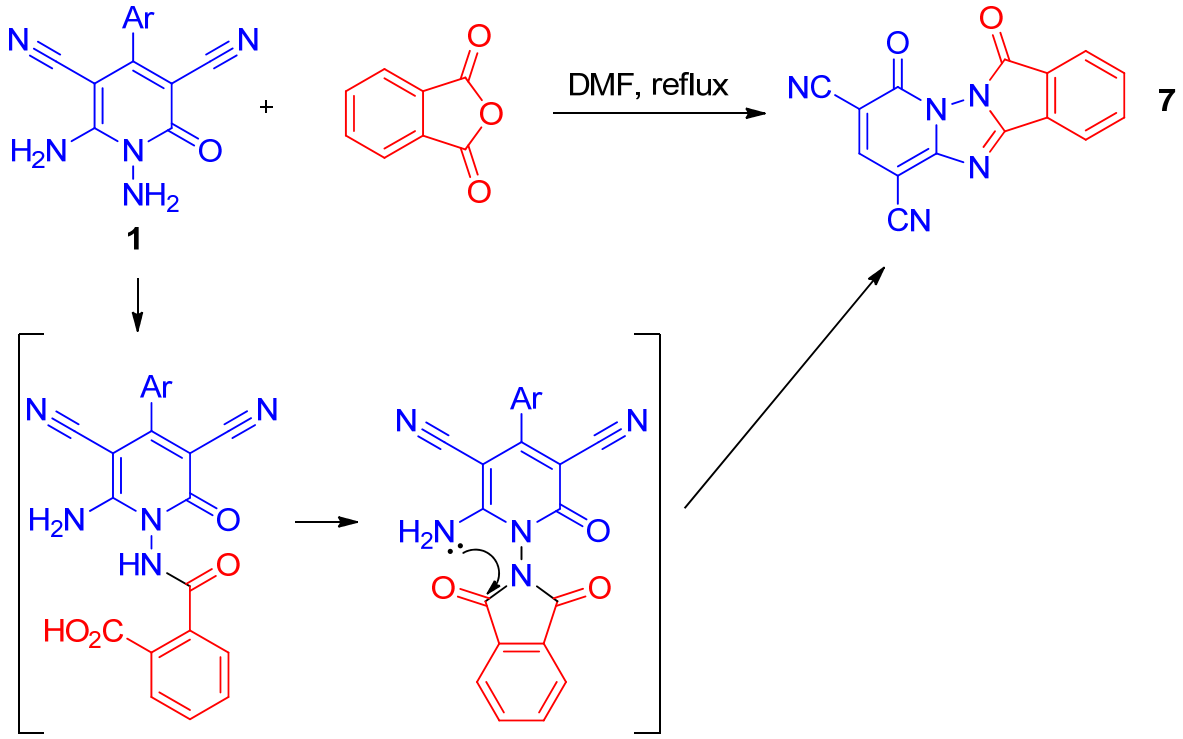
Scheme 2. The preparation of 1-cyanoacetyl-3,5-dimethylpyrazole **4**.

When 1,6-diamino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles **1** were treated with 1-cyanoacetyl-3,5-dimethylpyrazole **4** in hot AcOH, corresponding cyanoacetamides **5** were isolated in fair yields (Scheme 3). Similar results were observed in the reaction of **1** with chloroacetyl chloride—the products were corresponding chloroacetamides **6**. Compounds **5** and **6** can be considered as promising reagents for heterocyclic synthesis.



Scheme 3. The preparation of compounds **5** and **6**.

The reaction of 1,6-diaminopyridines **1** with phthalic anhydride proceeds in quite a different manner. Thus, when treated with an excess of phthalic anhydride in boiling DMF (dimethylformamide), derivatives of the new polyheterocyclic system—4,7-dioxo-4,7-dihydropyrido[1′,2′:2,3][1,2,4]triazolo[5,1-a]isoindole-1,3-dicarbonitrile **7**—were isolated. Presumably, the reaction started as simple acylation followed by cascade condensation to phthalimide and finally to polycyclic structure **7**.



Scheme 4. The preparation and mechanism of formation of compound **7**.

3. Experimental

Preparation of Compounds **5** *and* **6**

First, 1,6-Diamino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile **1** and 1.5 eq. 1-cyanoacetyl-3,5-dimethylpyrazole **4** were heated under reflux in a minimal amount of glacial AcOH. The reaction was monitored by TLC (thin-layer chromatography). After total consumption of **1**, the reaction refluxed for 5 min, and the product was allowed to cool and left to stand overnight. A yellowish solid was separated, filtered off and washed with EtOH to give pure cyanoacetamides **5.** A similar procedure as reported with chloroacetyl chloride afforded chloroacetamides **6**.

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Conflicts of Interest: The authors declare no conflict of interest.

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