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On the acylation of 1,6-diamino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles

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Abstract

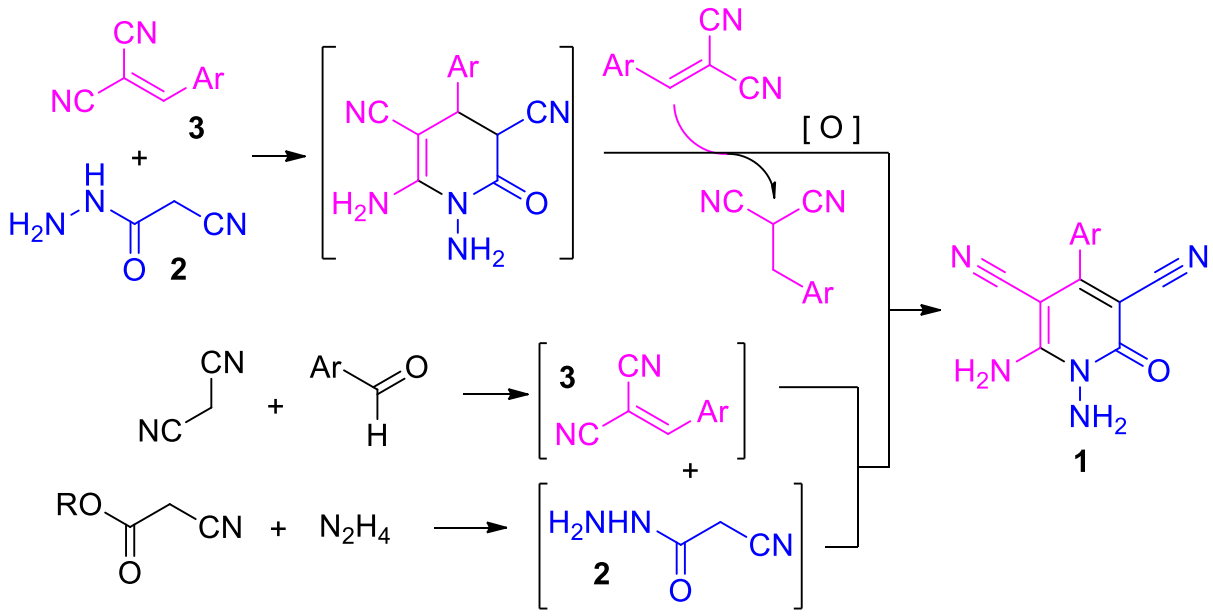
1,6-Diamino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles, prepared by reaction of cyanoacethydrazide with arylmethylene malononitriles, react with 1-cyanoacetyl-3,5-dimethylpyrazole and chloroacetyl chloride to give corresponding cyanoacetamides and chloroacetamides. The reaction with phthalic anhydride proceed 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.

1. Introduction

1,6-Diamino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles **1** were first prepared by Soto and colleagues as back as in 1981 through the reaction of cyanoacethydrazide **2** with 2 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 to build various nitrogen-bridged polyheterocyclic systems (for review, see [2]). A survey of literature revealed the 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. So we decided to fill the gap by ourselves to perform the aforementioned reactions.

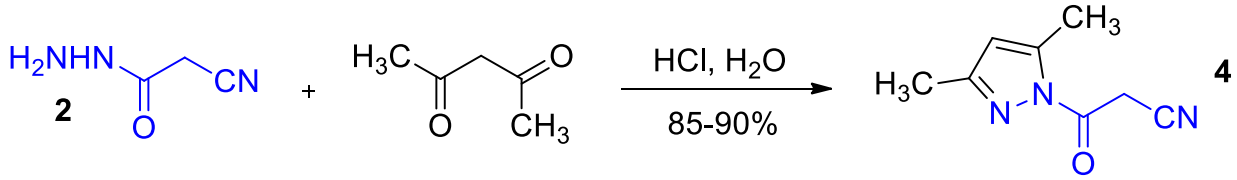


Scheme 1. The preparation of 1,6-diamino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles **1**.

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 reached only when arylmethylene malononitriles **3** were taken in at least two-fold excess with respect to cyanoacethydrazide **2**. Thus, the real oxidant in the reaction is arylmethylene malononitrile **3**, not atmosphere oxygen.

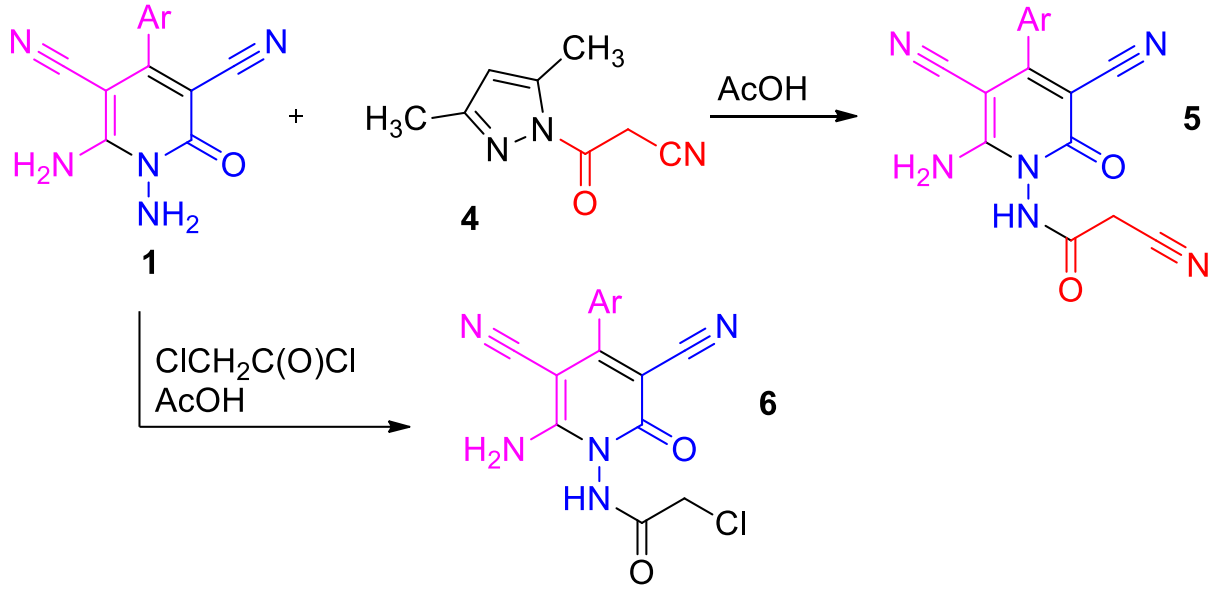
1-Cyanoacetyl-3,5-dimethylpyrazole **4** (3-(3,5-dimethyl-1H-pyrazol-1-yl)-3-oxopropanenitrile, cyanoacetylpyrazole), was introduced into synthetic practice by Ried and Meyer in 1957 [3] and since then it has established itself as highly effective cyanoacetylating agent – more powerful than ethyl cyanoacetate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



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

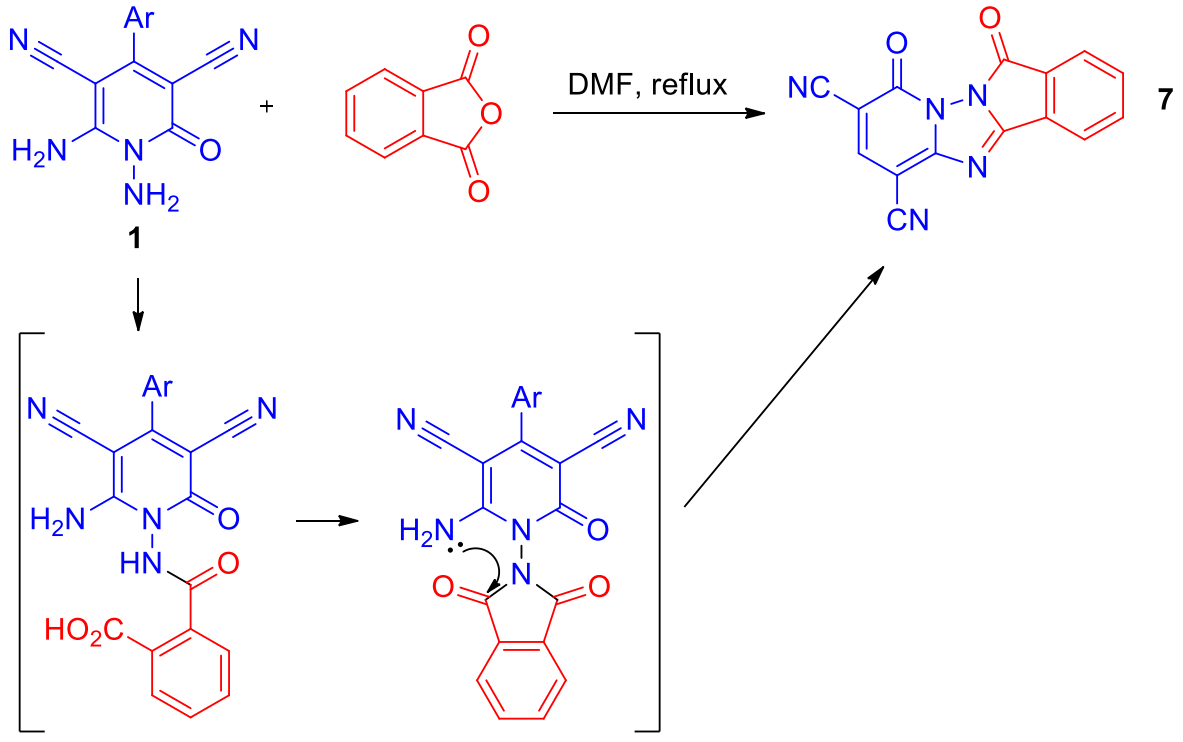
When 1,6-diamino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles **1** were treated with 1-cyanoacetyl-3,5-dimethylpyrazole **4** in hot AcOH, corresponding cyanoacetamides **5** were isolated in fair yields (Scheme 3). Similar results were

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 a quite different way. Thus, when treated with excess of phthalic anhydride in boiling DMF, derivatives of 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**.*

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 minimum amount of glacial AcOH. The reaction was monitored by TLC. After total consumption of **1** the reaction refluxed for 5 min, allowed to cool and left to stand overnight. A yellowish solid separated was filtered off and washed with EtOH to give pure cyanoacetamides **5.** Similar procedure reported with chloroacetyl chloride afforded chloroacetamides **6**.

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