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# Synthesis and Aminomethylation of 6-Amino-2-(dicyanomethylene)-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile Morpholinium Salt †

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**Abstract:** Condensation of benzaldehyde with malononitrile and malononitrile dimer (2-aminopropene-1,1,3-tricarbonitrile) in the presence of an excess of morpholine in ethanol afforded the morpholinium salt of 6-amino-2-(dicyanomethylene)-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile. The latter, under the Mannich reaction conditions with the participation of primary amines and formaldehyde, gives 6-amino-2-(dicyanomethylene)-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile, 2-(dicyanomethylene)-6-(hydroxymethylamino)-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile or zwitterionic aminomethylation products, 6-(ammoniomethylamino)-3,5-dicyano-4-phenylpyridin-2-yl)dicyanomethanides. Structure of the obtained compounds was established using 2D NMR spectroscopy and single crystal X-ray diffraction analysis.

**Keywords:** malononitrile dimer; 2-(dicyanomethylene)-1,2-dihydropyridines; aminomethylation; Mannich reaction

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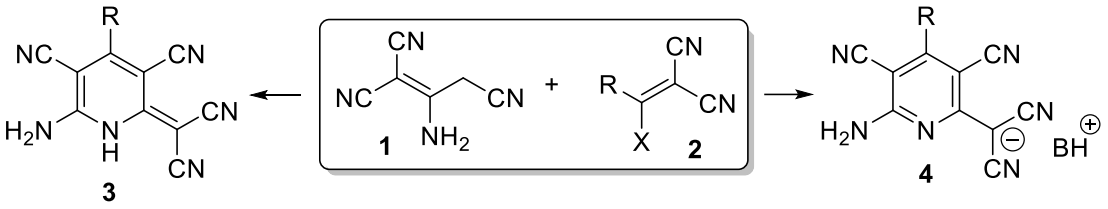
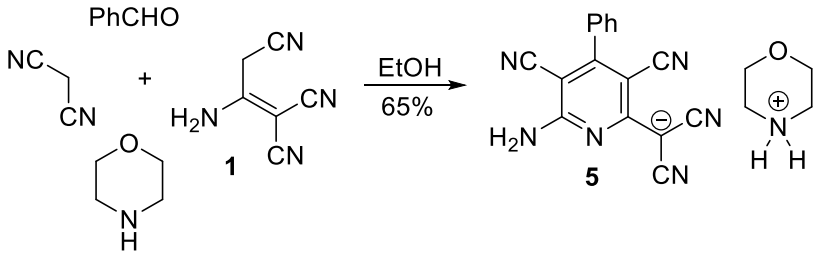
## 1. Introduction

One of the important directions of using malononitrile dimer is the synthesis of functionally substituted heterocyclic compounds—polycyanopyridines [1]. Such compounds are of interest as promising fluorescent dyes [2], antitumor kinase inhibitors [3], etc. In general, the synthesis of 6-amino-2-(dicyanomethylene)-1,2-dihydropyridine-3,5-dicarbonitriles **3** or their salts **4** includes the reaction of malononitrile dimer **1** with unsaturated dinitriles **2** [4–6] (Scheme 1).

6-Amino-2-(dicyanomethylene)-1,2-dihydropyridine-3,5-dicarbonitriles **3** were not introduced earlier into the aminomethylation reaction. Continuing our studies in the field of heterocyclization reactions with the participation of malononitrile dimer [7,8], we studied the behavior of compounds **3**, **4** analogs in the Mannich reaction. It was found that the sequential reaction of benzaldehyde, malononitrile, malononitrile dimer **1** in the presence of an excess of morpholine in ethanol at 25 °C leads to the formation of 6-amino-4-phenyl-2-(dicyanomethylene)-1,2-dihydropyridine-3,5-dicarbonitrile morpholinium salt **5** (R = Ph) in 65% yield (Scheme 2).



**Scheme 1.**

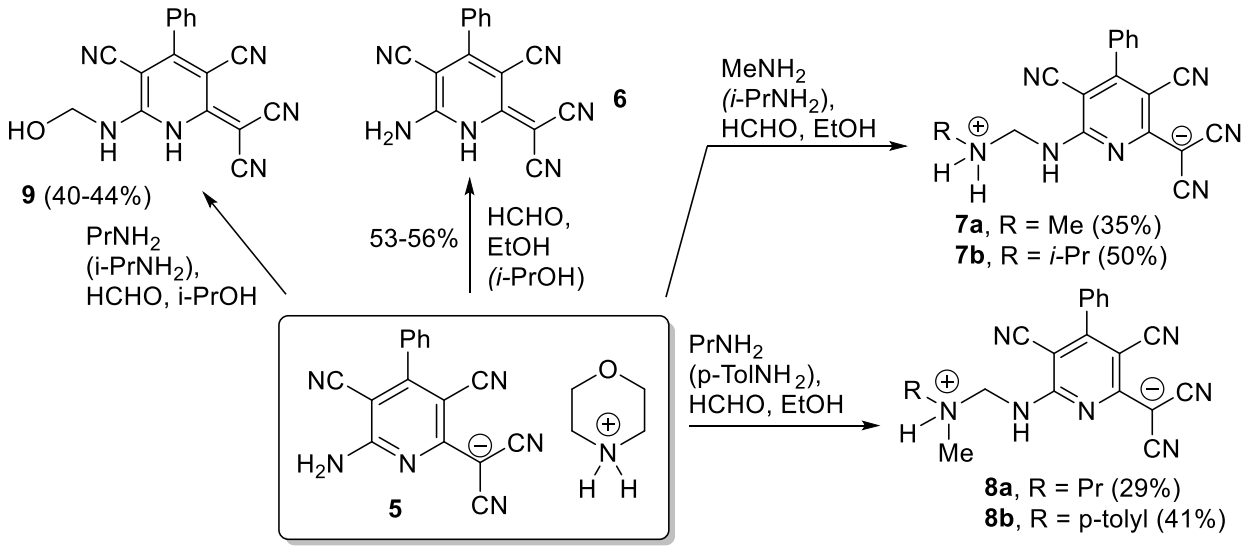


**Scheme 2.**

## 2. Results and Discussion

It was found that short-term boiling of salt **5** with an excess of formalin in EtOH or *i*-PrOH leads to the formation of 6-amino-4-phenyl-2-(dicyanomethylene)-1,2-dihydropyridine-3,5-dicarbonitrile **6** with yield of 53 or 56%, respectively, instead of the formation of oxy- or aminomethylation products. Refluxing salt **5** with an excess of HCHO, methylamine, or isopropylamine in EtOH yielded C6NH2 aminomethylation products **7a** and **7b** in 35 and 50% yields (Scheme 4). At the same time, carrying out the Mannich reaction under similar conditions, but with the participation of propylamine or *para*-toluidine, is accompanied by the Eschweiler–Clarke methylation reaction [22, 23] with the formation of betaines **8a** and **8b** (29 and 41% yields). When isopropanol is used as a solvent, the reaction of salt **5** with an excess of HCHO and propylamine or isopropylamine gives only pyridine **9** (40 and 44% yields) as the product of hydroxymethylation at the C6NH2 amino group.

Structure of compounds **5–9** was studied using 1H and 13C NMR spectroscopy (DEPTQ), two-dimensional 2D NMR experiments (1H–13C HSQC, 1H–13C HMBC, 1H–15N HSQC, 1H–15N HMBC), as well as IR spectroscopy. In addition, structure of compound **8a** was confirmed by single crystal X-ray diffraction analysis.



**Scheme 3.**

## 3. Experimental

General procedure for the synthesis 6-Amino-4-phenyl-2-(dicyanomethylene)-1,2-dihydropyridine-3,5-dicarbonitrile morpholinium salt (5):

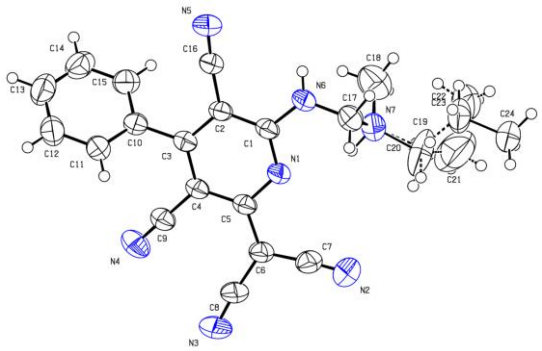
A mixture of 0.77 mL (7.5 mmol) of benzaldehyde, 0.5 g (7.5 mmol) of malononitrile, and 1 drop of morpholine in 25 mL of ethanol was stirred at 25 °C. After 10 min, 1.0 g (7.5 mmol) of malononitrile dimer **1** and 1.3 mL (15 mmol) of morpholine were added. After the dissolution of all the starting components, the reaction mixture was kept for 12 h, then the formed precipitate was filtered off, washed with cold ethanol and acetone, and dried at 60 °C within 3 h.

General procedure for the synthesis of 6-Amino-4-phenyl-2-(dicyanomethylene)-1,2-dihydropyridine-3,5-dicarbonitrile (6).

To a suspension of 0.74 g (2 mmol) of salt **10** in 20 mL of ethanol or isopropanol was added 3.5 mL of 37% HCHO. The reaction mixture was heated to boiling (homogenization occurred) and filtered through a paper filter. The formed precipitate was separated after 24 h, washed with cold ethanol, and dried at 60 °C within 3 h.

General procedure for the synthesis of compounds **7–9**:

A mixture of 0.74 g (2 mmol) of salt **5**, 2 mmol of the corresponding primary amine, 3.5 mL of 37% HCHO in 20 mL of ethanol (or isopropanol for compound **9**) was brought to a boil and homogenized, then filtered through a paper filter. The formed precipitate was separated after 24 h, washed with cold ethanol, and dried at 60 °C within.




General view of the molecule of compound **8a** in the crystal.

**Institutional Review Board Statement:**

**Informed Consent Statement:**

**Data Availability Statement:**

## References

1. Ershov, O.V.; Bardasov, I.N. Synthesis of pyridine derivatives containing a tricyanobutadiene motif (microreview). *Chem. Heterocycl. Compd*. **2017**, *53*, 1178.
2. Bardasov, I.N.; Alekseeva, A.U.; Chunikhin, S.S.; Tafeenko, V.A.; Ershov, O.V. Three-component synthesis and optical properties of triarylpyridines containing a buta-1, 3-diene-1, 1, 3-tricarbonitrile fragment. *Tetrahedron Lett*. **2017**, *58*, 3919.
3. Mohareb, R.M.; Abouzied, A.S.; Abbas, N.S. Synthesis of Pyridine and Spiropyridine Derivatives Derived from 2-aminoprop-1-ene-1, 1, 3-tricarbonitrile Together with their c-Met Kinase and Antiproliferative Evaluations. *Anti-Cancer Agents Med. Chem*. **2017**, *17*, 1951.
4. Fuentes, L.; Vaquero, J.J.; Soto, J.L. *Synthesis* **1982**, 320.
5. Helmy, N.M.; El-Baih, F.E.M.; Al-Alshaikh, M.A.; Moustafa, M.S. A route to dicyanomethylene pyridines and substituted benzonitriles utilizing malononitrile dimer as a precursor. *Molecules* **2011**, *16*, 298.
6. Fuentes, L.; Márquez, C.; Contreras, M.C.; Lorenzo, M.J.; Fonseca, I.; Sanz-Aparicio, J.; Balcazar, J.L. Synthesis and structure of new substituted 2-dicyanomethylene-1, 2-dihydropyridines. *J. Heterocycl. Chem*. **1995**, *32*, 29.
7. Dotsenko, V.V.; Chigorina, E.A.; Krivokolysko, S.G. Synthesis of derivatives of a novel heterocyclic system 7-thia-1, 4, 6, 8-tetraazabenzo [de] anthracene. *Chem. Heterocycl. Compd*. **2017**, *53*, 626.
8. Dotsenko, V.V.; Bespalov, A.V.; Russkikh, A.A.; Kindop, V.K.; Aksenov, N.A.; Aksenova, I.V.; Shcherbakov, S.V.; Ovcharov, S.N. Reactions of Malononitrile Dimer with Isothiocyanates. *Russ. J. Gen. Chem.* **2021**, *91*, 951.