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Proceeding Paper

New Methods of Synthesis, Structure and Aminomethylation of 4-Imino-2-(dicyanomethylene)-3-azaspiro[5.5]undecane1,5-dicarbonitrile †

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Abstract: Sequential reaction of cyclohexanone with malononitrile and 2-aminopropene-1,1,3-tricarbonitrile in potassium hydroxide or sodium ethylate in ethanol gave 4-imino-2-(dicyanomethylene)-3-azaspiro[5.5]undecane-1,5-dicarbonitrile.The latter reacts with primary amines and an excess of formaldehyde to form new derivatives of 2-(dicyanomethylene)-3,7-diazaspiro[bicyclo[3.3.1]non-3-ene-9,1′-cyclohexane] -1,5-dicarbonitrile. Contrary to the literature data, the reaction of cyclohexanone with 2-aminopropene-1,1,3-tricarbonitrile in benzene in the presence of piperidine and glacial acetic acid led to the formation of 2,4-diamino-5,6,7,8-tetrahydronaphthalene-1,3-dicarbonitrile.

Keywords: cyclohexanone; malononitrile; 2-aminopropene-1,1,3-tricarbonitrile; 2,4-diamino-5,6,7,8-tetrahydronaphthalene-1,3-dicarbonitrile; 4-imino-2-(dicyanomethylene)-3-azaspiro[5.5]undecane-1,5-dicarbonitrile; aminomethylation

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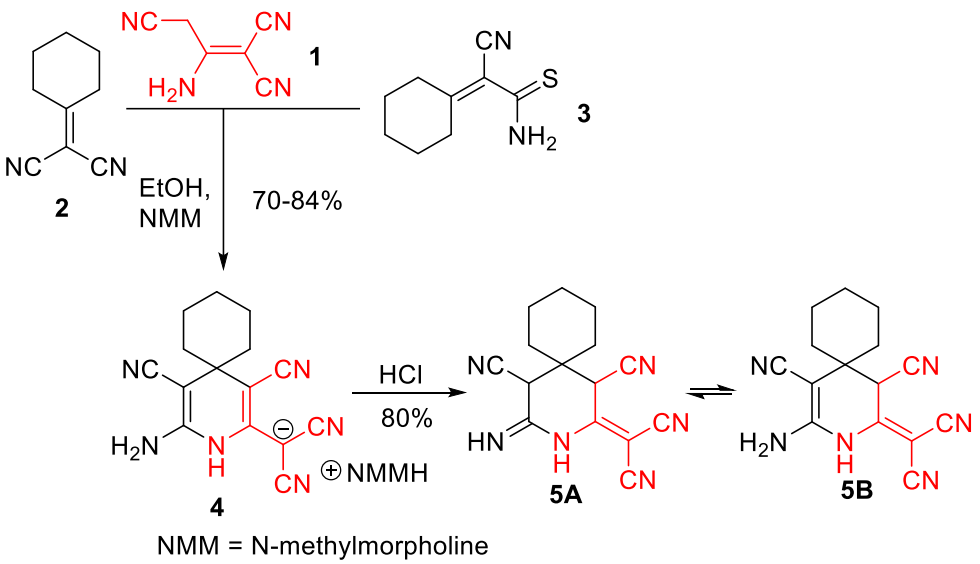
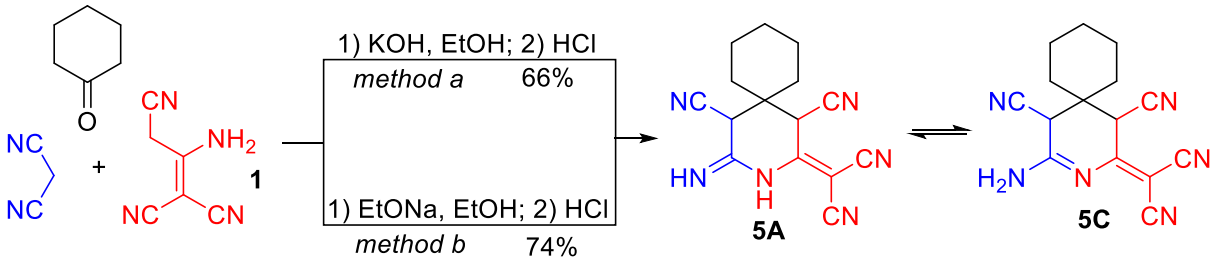
1. Introduction

Malononitrile dimer (2-aminopropene-1,1,3-tricarbo-nitrile) **1** is used as a multifunctional reagent in the synthesis of various carbo- and heterocyclic compounds [1,2]. It has been previously shown that cyclohexanone derivatives, unsaturated nitriles **2** and **3**, react readily with malononitrile dimer **1** in ethanol in the presence of N-methylmorpholine (NMM) with the formation of salt **4** in 84 and 70% yields, respectively (Scheme 1) [3]. Upon acidification of salt **4** with hydrochloric acid, 4-imino-2-(dicyanomethylene)-3-azaspiro[5.5]-undecane-1,5-dicarbonitrile **5** was obtained in 80% yield. In a DMSO solution, dicarbonitrile **5** exist as a mixture of imine and amine tautomers **5A** and **5B** in a ratio of ~1:1 (Scheme 1) [3].

Continuing our research in the field of malononitrile dimer chemistry [4–7], we developed new convenient approaches to the synthesis of compound **5** and studied the possibility of obtaining new polynitrile compounds based on it. We found that after the sequential reaction of cyclohexanone and malononitrile with malononitrile dimer **1** in ethanol in the presence of KOH (method a) or EtONa (method b) and further acidification of the reaction mixture with HCl, compound **5** is formed in 66 and 74% yields, respectively (Scheme 2).



Scheme 1

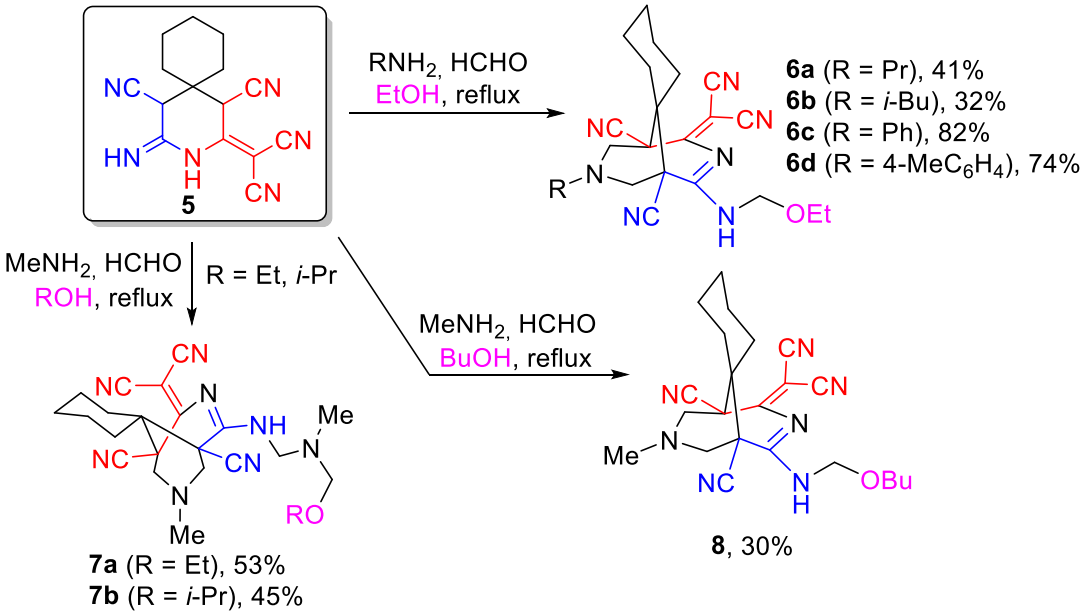


Scheme 2

2. Results and Discussion

Upon aminomethylation of compound **5** under conditions excess of HCHO, 2 equiv. of primary amine, refluxing in alcohol, using various alcohols (EtOH, i-PrOH, or n-BuOH) as solvents, we obtained new 2-(dicyanomethylene)-3,7-diazaspiro[bicyclo[3.3.1]non3-ene-9,1′-cyclohexane]-1,5-dicarbonitrile derivatives **6**–**8** in yields of 32–53% (when using aliphatic amines) and 74–82% (in the case of aryl amines) (Scheme 3). Interestingly that regardless of the nature of the amines and solvents used, the expected closure of the 1,3,5-triazine ring does not occur. In our opinion, a possible reason for this may be the strong electronwithdrawing effect of the dicyanomethylene fragment and, as a consequence, the decreased nucleophilicity of the conjugated endocyclic nitrogen atom.

Structure of the obtained compounds was proved using 1H and 13C NMR spectroscopy (DEPTQ, 1H–13C HSQC, 1H–13C HMBC, 1H–15N HSQC), IR spectroscopy. In addition, structure of compounds **6** and **7** was studied using the single crystal X-diffraction analysis method. Unlike compound **5**, derivatives **6**–**8**, both in crystalline form and in DMSO solutions, exist as a single tautomeric form.



Scheme 3

3. Experimental

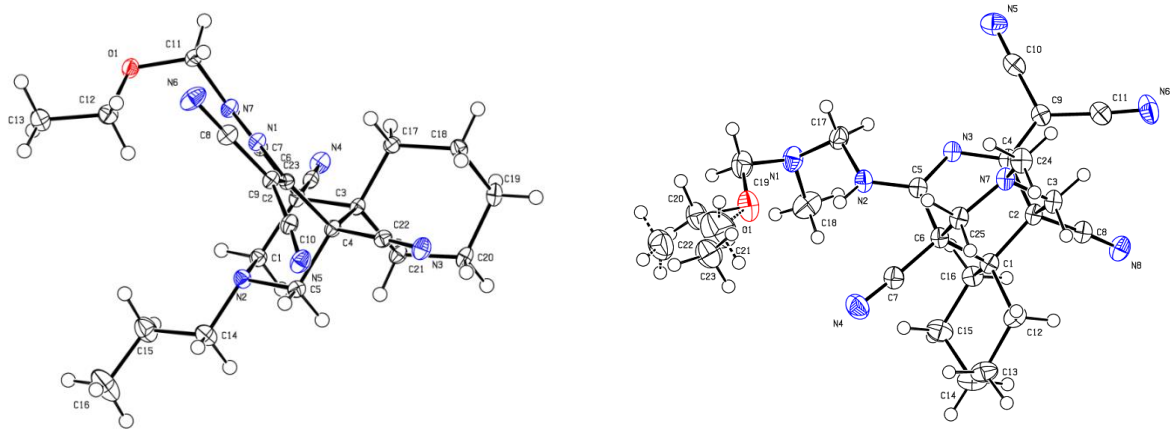
General procedure for the synthesis 4-Imino-2-(dicyanomethylene)-3-azaspiro[5.5]undecane-1,5-dicarbonitrile (5).

a. To a solution of 0.64 g (11.3 mmol) of KOH in 20 mL of 96% ethanol was added 1.00 g (7.5 mmol) of malononitrile dimer 1. In another reaction vessel, 0.78 mL (7.5 mmol) of cyclohexanone and 0.75 g (11.3 mmol) of malononitrile were added to a solution of 0.32 g (5.7 mmol) of KOH in 15 mL of 96% ethanol; the resulting mixture was stirred for 10 min at 20°C, then added to the first vessel and stirred for 2 h. To the resulting pale yellow precipitate, 40 mL of water was added until complete dissolution. Next, the reaction mixture was treated with conc. HCl to pH 3–4. The formed precipitate was filtered off after 12 h, washed with cold ethanol, and dried for 3 h at 60 °C.

b. The synthesis was performed similarly to method a with the same loadings, only with using absolute ethanol, 0.26 g (11.3 mmol) and 0.13 g (5.7 mmol) of sodium. Yield 74%, the product is identical to the sample prepared by method *a*.

General procedure for the synthesis of spiro[bicyclo[3.3.1]non-3-ene-9,1′-cyclohexane]-1,5dicarbonitriles **6**-**8**:

A mixture of 0.56 g (2 mmol) of compound **5**, 4 mmol of the corresponding primary amine and an excess (3–4 mL) of 37% formalin in 20 mL of the corresponding alcohol (EtOH, i-PrOH, or n-BuOH) was boiled for 1–5 min until complete homogenization. The resulting solution was filtered through a filter paper and kept for 24 h at 20 °C. The precipitate was filtered off, washed with ethanol and dried for 3 h at 60 °C.



(**a**) (**b**)

Figure 1. (**a**) General view of the molecule of compound **6a** in the crystal. (**b**) General view of the molecule of compound **7a** in the crystal.

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References

1. Dotsenko, V.V.; Krivokolysko, S.G.; Semenova, A.M. Heterocyclization reactions using malononitrile dimer (2-aminopropene-1,1,3-tricarbonitrile). *Chem. Heterocycl. Compd.* **2018**, *54*, 989–1019.
2. Shaabani, A.; Hooshmand, S.E. *Mol. Divers.* **2018**, 207.
3. Dyachenko, V.D.; Litvinov, V.P. *Doklady Chem.* **1997**, *355*, 153.
4. Dotsenko, V.V.; Chigorina, E.A.; Krivokolysko, S.G. *Chem. Heterocycl. Compd.* **2017**, *53*, 626.
5. Dotsenko, V.V.; Krivokolysko, S.G.; Chernega, A.N.; Litvinov, V.P. *Russ. Chem. Bull.* **2003**, *52*, 969.
6. Dotsenko, V.V.; Krivokolysko, S.G.; Litvinov, V.P.; Chernega, A.N. *Chem. Heterocycl. Compd.* **2007**, *43*, 599.
7. Semenova, A.M.; Oganesyan, R.V.; Dotsenko, V.V.; Chigorina, E.A.; Aksenov, N.A.; Aksenova, I.V.; Netreba, E.E. *Russ. J. Gen. Chem.* **2019**, *89*, 19.