chemistry proceedings

MDPI

Proceedings Paper

Synthesis of 1-amino-5-cyano-2-oxo-1,2-dihydronicotic acid †

Victor V. Dotsenko1,2,3*, Alena A. Russkih1, Nikolai A. Aksenov3 and Inna V. Aksenova3, Inessa A. Efimova4

1 Department of Chemistry and High Technologies, Kuban State University, 149 Stavropolskaya str, Krasnodar 350040, Russia; alena.russkih.19988@gmail.com
2 ChemEx Lab, Department of Chemistry, 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; radioanimation@rambler.ru (N.A.A.); inna-aksenova00@rambler.ru (I.V.A.)
4 Russian University of Chemical Technology named after D. I. Mendeleev, Miusskaya pl., 9,Moscow, Russia.
* Correspondence: victor_dotsenko_@mail.ru
† Presented at the 25th International Electronic Conference on Synthetic Organic Chemistry, 15–30 November 2021; Available online: https://ecsoc-25.sciforum.net/.

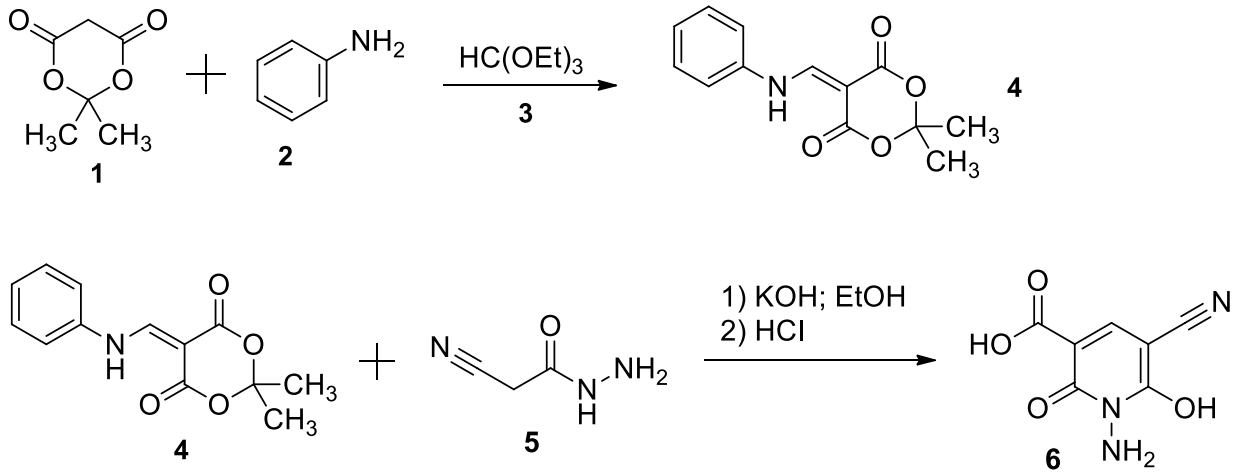
Abstract: 2,2-Dimethyl-5-((phenylamino)methylene)-1,3-dioxane-4,6-dione, prepared by ternary condensation of Meldrum's acid with triethyl orthoformate and aniline, reacts with cyanoacetic acid hydrazide in the presence of KOH to give 1-amino-5-cyano-2-oxo-1,2-dihydropyridine-3-carboxylic acids, which are useful as drug precursors or perspective ligands.

Keywords: nicotinic acids; Meldrum's acid; 1-amino-5-cyano-2-oxo-1,2-dihydronicotic acid, cyanoacetic acid hydrazide.

1. Introduction

It is known that nicotinic acid (pyridine-3-carboxylic acid, niacin, vitamin PP, vitamin B3) and nicotinic acid derivatives have a wide spectrum of biological activity. Thus, nicotinic acid and nicotinates exhibit hypocholesterolemic, neuroprotective and other effects. The close structural analogue of nicotinic acid, 4-methyl-2-oxo-5-cyano-1,2-dihydropyridine-3-carboxylic acid, is less studied and is of interest as a complexing agent [1,2] or as a precursor for biologically active compounds [3].

We have developed a method for preparation of substituted 2-oxonicotinic acids based on the reaction of 5-anilinomethylidene-2,2-dimethyl-1,3-dioxane-4,6-dione 4 with cyanoacetamides 5. Compound 4 was prepared by reaction of Meldrum's acid 1 with triethyl orthoformate 3 and aniline 2. The reaction of 4 with cyanoacethydrazide 5 (R = NH2) afforded 1-amino-5-cyano-2-oxo-1,2-dihydronicotic acid 6. The structure was confirmed by means of FTIR, NMR and X-ray data.



Scheme 1. Preparation of 1-amino-5-cyano-2-oxo-1,2-dihydronicotic acid 6.

In order to cast light on the possible extension of this Knoevenagel/cation approach for the development of new, highly-fluorescent photo-theragnostic agents based on selective accumulation into mitochondria, this communication describes preliminary results on the use of different cations (specifically, trimethylammonium) and spacers.

2. Experimental

2.1. Anilinomethylidene Derivative of Meldrum's Acid

A mixture of the powdered Meldrum's acid (0.1 mol), triethyl orthoformate (21.6 mL, 0.13 mol), and freshly distilled aniline (9.1 mL, 0.1 mol) was refluxed with vigorous stirring for 5 min to afford a syrupy reaction mass. It was diluted with 30 mL of EtOH and refluxed for an additional 3 min. Then, it was cooled with stirring to ~20 °C and diluted with water to 100 mL. After 2 h, the product was filtered off and washed with water, twice with 60% EtOH, and with hexane.

2.2. 2,2-Dimethyl-5-(Phenylamino)Methylene-1,3-Dioxane-4,6-Dione (4)

Yield 92%, m.p. 156–157 °C. Found (%): C, 63.19; H, 5.32; N, 5.66. C13H13NO4. Calculated (%): C, 63.15; H, 5.30; N, 5.67. 1H NMR, δ: 1.70 (s, 6 H, 2 Me); 7.19-7.51 (m, 5 H, Ph); 8.58 (d, 2 H, –CH =, 3J = 14.7 Hz); 11.27 (d, 1 H, NH, 3J = 14.7 Hz).

2.3. Compounds 6

Potassium hydroxide (1.12 g, 0.02 mol) was added to a vigorously stirred suspension of compound 4 (0.01 mol) and cyanoacetic acid hydrazide (0.01 mol) in 10 mL of EtOH. After 24 h, the reaction mixture was acidified with concentrated HCl to pH 5 and maintained for 3 h. The formed precipitate was recrystallized from water. The yield of pyridine 6 was 65%.

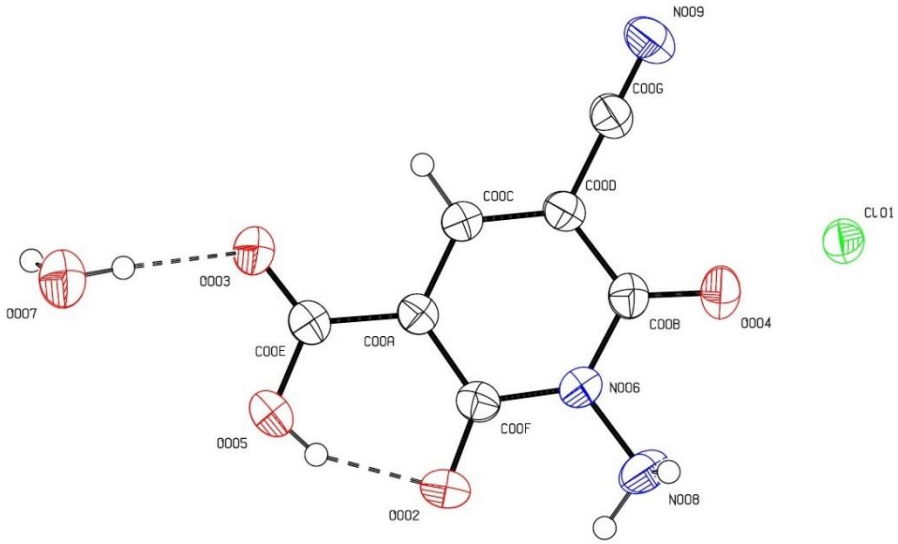


Figure 1. Molecular Structure of compound 6 (X-ray data).

References

1. Di Marco, V.B.; Tappro, A.; Dolmella, A.; Bombi, G.G. Complexation of 2-hydroxynicotinic and 3- hydroxypicolinic acids with zinc (II). Solution state study and crystal structure of trans-diaqua-bis-(3-hydroxypicolinato) zinc(II). Inorg. Chim. Acta 2004, 357, 135–142.
2. Yoshito, O.; Fumiaki, H.; Yoshihiro, T.; Takayasu, K. Studies on the interaction of pyridone carboxylic acids with metals. Chem. Pharm. Bull. 1992, 40, S692–S696.
3. Fossa, P.; Menozzi, G.; Dorigo, P.; Floreani, M.; Mosti, L. Synthesis and pharmacological characterization of functionalized 2-pyridones structurally related to the cardiotonic agent milrinone. Bioorg. Med. Chem. 2003, 11, 4749–4759. 4. Dotsenko, V.V.; Krivokolysko, S.G.; Chernega, A.N.; Litvinov, V.P. Anilinomethylidene derivatives of cyclic 1,3-dicarbonyl compounds in the synthesis of new sulfur-containing pyridines and quinolines. Russ. Chem. Bull. 2002, 51, 1556–1561Jiménez, J.; Díaz-Norambuena, C.; Serrano, S.; Ma, S.C.; Moreno, F.; Maroto, B.L.; Bañuelos, J.; Muller, G.; Moya, S. de la. BINOLated Aminostyryl BODIPYs: A Workable Organic Molecular Platform for NIR Circularly Polarized Luminescence. *Chem. Commun.* **2021**, *57*, 5750–5753.