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Synthesis of New 2-Oxo-1,2-Dihydropyridine-3-Carboxylic Acid Derivatives †

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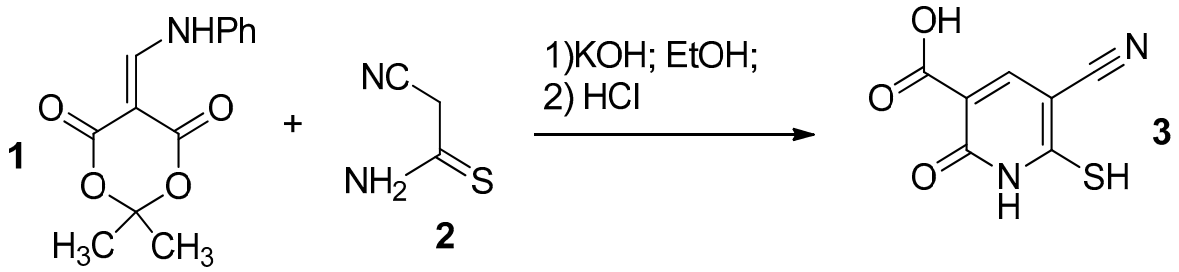
Abstract: 2,2-Dimethyl-5-((phenylamino)methylene)-1,3-dioxane-4,6-dione, prepared by the reaction of Meldrum's acid with triethyl orthoformate and aniline, reacts with active methylene nitriles to afford 2-oxo-1,2-dihydropyridine-3-carboxylic acid derivatives, which are useful as drug precursors or perspective ligands.

Keywords: nicotinic acids; Meldrum's acid; 2-oxo-1,2-dihydropyridine-3-carboxylic acid; cyanothioacetamide; cyanoacetamide

1. Introduction

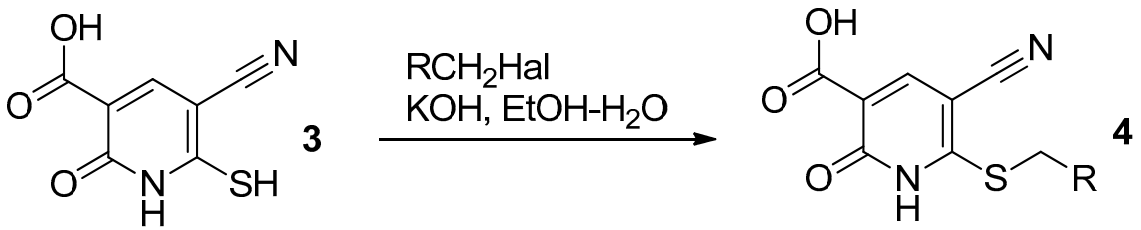
It is known that nicotinic acid (niacin, vitamin PP) and its derivatives have a wide spectrum of biological activity. Thus, nicotinic acid and nicotinates have showed hypolipidemic, hypocholesterolemic, neuroprotective and other effects. 2-Oxo-1,2-dihydropyridine-3-carboxylic acid is less studied; however, it is of interest as a complexating agent [1,2] and in pharmaceuticals [3].

Previously, we developed a method the for synthesis of 6-mercapto-2-oxonicotinic acid **3** based on the heterocyclization of aminomethylidene derivative of Meldrum's acid **1** with cyanothioacetamide **3** (Scheme 1) [4].



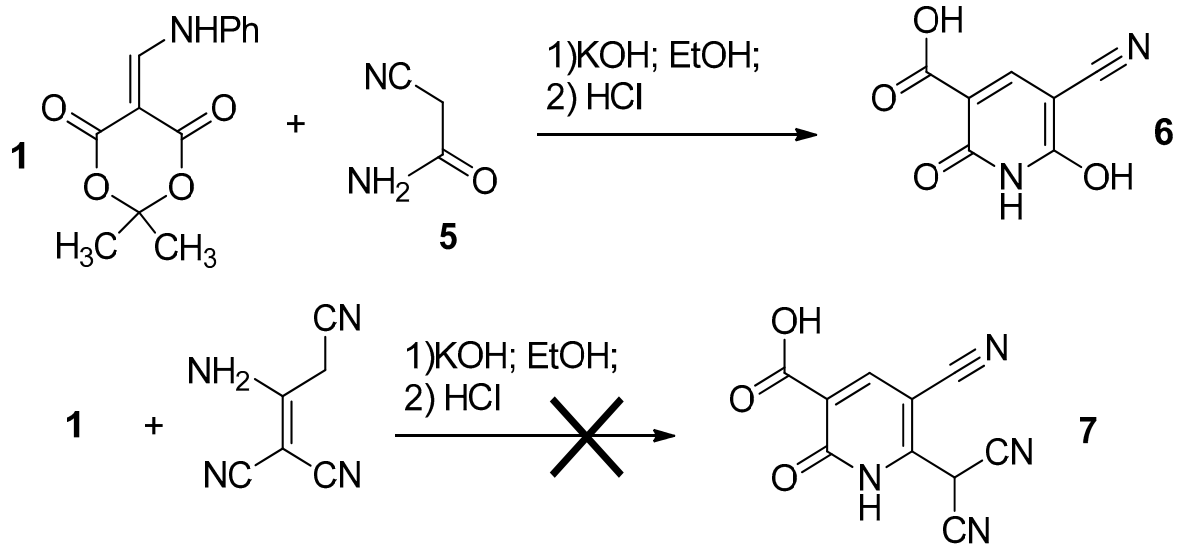
Scheme 1. The reaction of cyanothioacetamide with anilinomethylidene Meldrum's acid.

We decided to study the reactions of 5-cyano-2-oxo-1,2-dihydropyridine-3-carboxylic acid **3**. Compound **3** easily reacts with alkyl halides regioselectively at the S atom to give sulfides (Scheme 2) **4**.



Scheme 2. S-alkylation of compound 3.

Other active methylene nitriles were also introduced in the reaction. Thus, cyanoacetamide **5** in the presence of KOH reacts with enamino-1,3-diketone **1** followed by acidification to give pyridine **6** in a good yield (Scheme 3). However, we failed to prepare compound **7** starting from a malononitrile dimer.



Scheme 3. The reaction of anilinomethylidene Meldrum's acid with active methylene nitriles.

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 (1)

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. ^{1}H 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 3 and 6 (General Procedure)

Potassium hydroxide (1.12 g, 0.02 mol) was added to a vigorously stirred suspension of compound **1** (0.01 mol) and cyano(thio)acetamide (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 precipitate that formed was filtered off and washed successively with water and EtOH. The yield of pyridine **3** was 68% and that of pyridine **6** was 74%.

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