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Synthesis of New 2-Oxonicotinic acids

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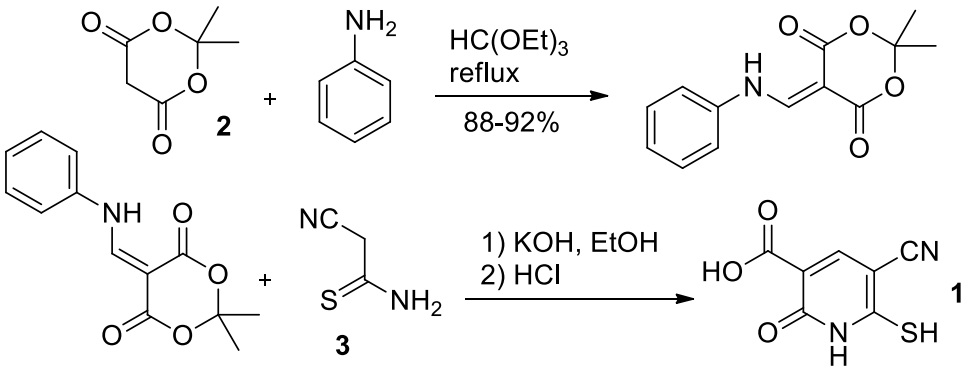
Abstract: 2,2-Dimethyl-5-((phenylamino)methylene)-1,3-dioxane-4,6-dione, prepared by ternary condensation of Meldrum's acid with triethyl orthoformate and aniline, reacts with N-aryl cyanoacetamides in the presence of KOH to give 2-oxo-1,2-dihydropyridine-3-carboxylic acids, which are useful as drug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

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

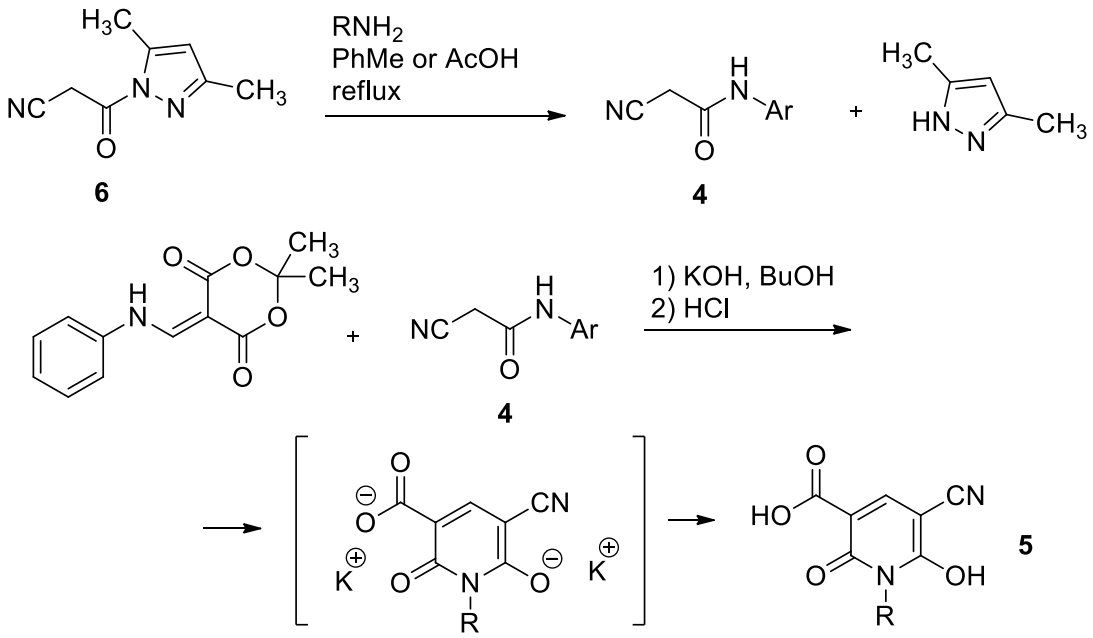
1. Introduction

Nicotinic acid (niacin, vitamin PP) and its derivatives have been recognized to have a wide spectrum of biological activity. Thus, nicotinic acid and derivatives were used for treatment of hyperlipoproteinemia, and posess hypocholesterolemic, neuroprotective, antitumor and other effects [1–4]. 2-Oxo-1,2-dihydropyridine-3-carboxylic acids are less studied; however, they are of interest as complexing agents [5,6] and as pharmaceuticals [7]. Earlier we described [8] the method for preparation of 5-cyano-6-mercapto-2-oxo-1,2-dihydropyridine-3-carboxylic acid **1** starting from Meldrum's acid **2** (for reviews see [9–14]) and cyanothioacetamide **3** [15,16] (Scheme 1).



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

Using N-substituted cyanoacetamides **4** instead of cyanothioacetamide **3**, we succeeded to prepare new N-aryl 2-oxonicotininc acids **5**. The reaction proceeds smoothly in the presence of KOH in alcohols. The treatment of the dipotassium salts formed liberated free acids **5** (Scheme 2). Cyanoacetamides **4** were prepared by cyanoacetylation of primary amines with cyanoacetylpyrazole **6** [17–19].



Scheme 2. The reaction of N-substituted 2-cyanoacetamides **4** with 2,2-dimethyl-5-(phenylamino)methylene-1,3-dioxane-4,6-dione.

2. Experimental

2.1. 2,2-Dimethyl-5-(phenylamino)methylene-1,3-dioxane-4,6-dione

A mixture of the powdered Meldrum's acid (14.0 g, 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. Yield 92%, m.p. 156–157 °C. Found (%): C, 63.19; H, 5.32; N, 5.66. $C_{13}H_{13}NO_4$. 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 =, ^{3}J = 14.7 Hz); 11.27 (d, 1 H, NH, ^{3}J = 14.7 Hz).

2.2. Compounds **5** *(General Procedure)*

Potassium hydroxide (0.45 g, 0.008 mol) was added to a vigorously stirred suspension of 2,2-dimethyl-5-(phenylamino)methylene-1,3-dioxane-4,6-dione (0.004 mol) and corresponding cyanoacetamide (0.004 mol) in 10 mL of EtOH (or BuOH). After 24 h, the slurry of deposited dipotassium salt was acidified with concentrated HCl to adjust pH value to 3.0 and maintained for 3 h. The precipitate formed was filtered off to give N-aryl 2-oxonicotininc acids **5**.

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