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The Aminometylation of 4-(Alkylthio)-6-Amino-2-oxo(thioxo)-1,2-Dihydropyridine-3,5-Dicarbonitriles †

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Abstract: Easily available 2-(bis(alkylthio)methylene)malononitriles react with cyanoacetamide or cyanothioacetamide to give 4-(alkylthio)-6-amino-2-oxo(thioxo)-1,2-dihydropyridine-3,5-dicarbonitriles. Upon treatment with primary amines and/or HCHO, the compounds undergo heterocyclization to afford new pyrido[1,2-a][1,3,5]triazines or ring-condensed 1,3,5,7-tetrazocine derivatives.

Keywords: 6-aminopyridin-2-ones; 2-thioxopyridines; mannich reaction; aminomethylation; heterocyclization; 1,3,5-triazines; tetrazocines

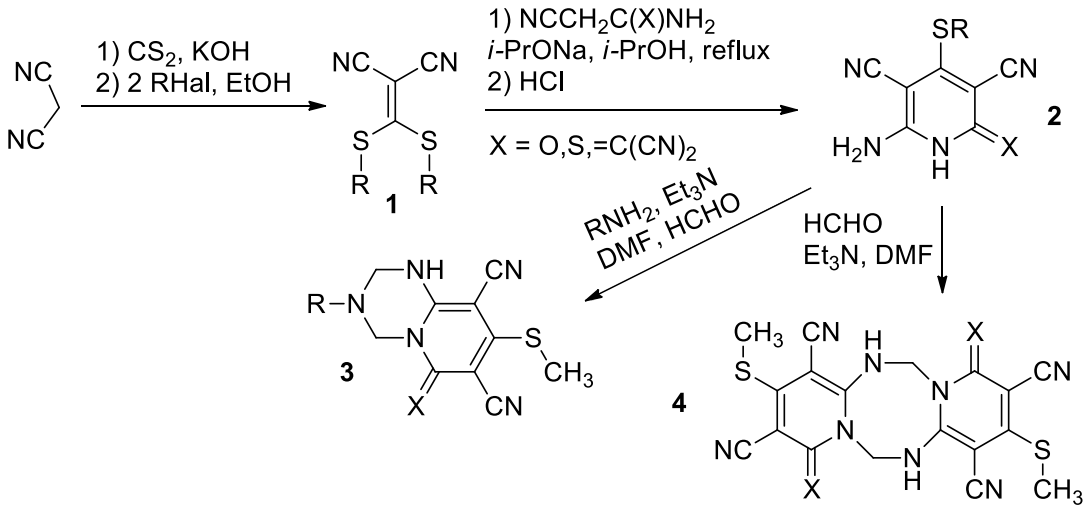
1. Introduction

Ketene-S,S-acetals derived from malononitrile (2-(bis(alkylthio)-methylene)malononitriles) are widely used in organic synthesis. These compounds readily react with various nucleophilic reagents, so they are often used for the synthesis of a number of heterocyclic compounds, such as pyrans, pyrroles, thiophenes, pyrazoles, pyridines and pyrimidines, etc. [1,2]. Ketene-S,S-acetals also show biological activity, they found an application in agriculture and medicine [1,2].

2. Results and Discussion

Aminomethylation of multifunctional heterocyclic substrates gives polycyclic products which are of interest as ligands or platform to build supramolecular systems. Earlier we reported [4–6] the aminomethylation reaction of 6-amino-3,5,-dicyano-2-thioxo(oxo)-1,2-dihydropyridines leading to pyrido[1,2-a][1,3,5]triazines useful as perspective herbicides. The aim of the presentt study is to prepare new pyrido[1,2-a][1,3,5]triazines starting from ketene-S,S-acetals.

We prepared ketenedithioacetals **1** from carbon disulfide and malononitrile by known method [3]. Next, the reaction of the prepared ketendithioacetals **1** with active methylene compounds—cyanoacetamide [7–9] or cyanothioacetamide [7,10] was performed. The reaction was carried out in i-PrOH in the presence of sodium isopropylate, followed by acidification with hydrochloric acid. The resulting 4-(alkylthio)-6-amino-2-oxo(thioxo)-1,2-dihydropyridine-3,5-dicarbonitriles **2** were treated with primary amines and HCHO. As a result, previously undescribed pyrido[1,2-a][1,3,5]triazines **3** were prepared. In the absence of primary amines, intermolecular aminomethylation occurs involving molecules **2** both as a substrate and as a aminomethylating agent predecessor to afford ring fused 1,3,5,7-tetrazocines **4** (Scheme 1).

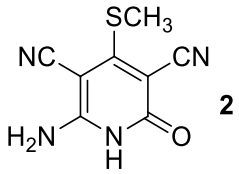


Scheme 1. The synthetic pathway to compounds **3** and **4**.

3. Experimental

The following representative examples of practical procedures are given:

3.1. 6-Amino-4-(methylthio)-2-oxo-1,2-Dihydropyridine-3,5-Dicarbonitrile (2)



Sodium metal (0.3 g, 0.013 mol) was dissolved in absolute isopropanol (30 mL) placed in a round-bottom flask equipped with a reflux condenser. To the resulted solution, 0.84 g (0.01 mol) of cyanoacetamide and 1.7 g (0.01 mol) of 2-(*bis* (methylthio)methylene)malononitrile **1** were added. The mixture was refluxed for 3.5 h (*Caution! Foul-smelling CH_3SH evolved!*). The precipitate of a sodium salt was filtered off, dissolved in water and treated dropwise with a solution of hydrochloric acid to adjust pH to 4.0. The precipitated solid was filtered off and washed with EtOH to give 1.1 g (53%) of 6-amino-4-(methylthio)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile. M.p. > 240 °C.

IR spectrum (ν, cm^{-1}): 3471 (NH); 2198 (2 CN); 1612 (C=C, C=N) (Figure 1).

NMR ^1H (δ, ppm, DMSO-d_6): 2.70 (s, 3H, SCH_3); 7.69 (br s, 2H, NH_2); 11.73 (br s, 1H, NH). NMR ^{13}C (δ, ppm, DMSO-d_6): 162.2 (C=O); 159.5 (C^6-NH_2); 156.5 (C^4); 116.2 (C≡N); 115.3 (C≡N); 90.2 (C^3-CN); 76.3 (C^5-CN); 17.9 (SCH_3).

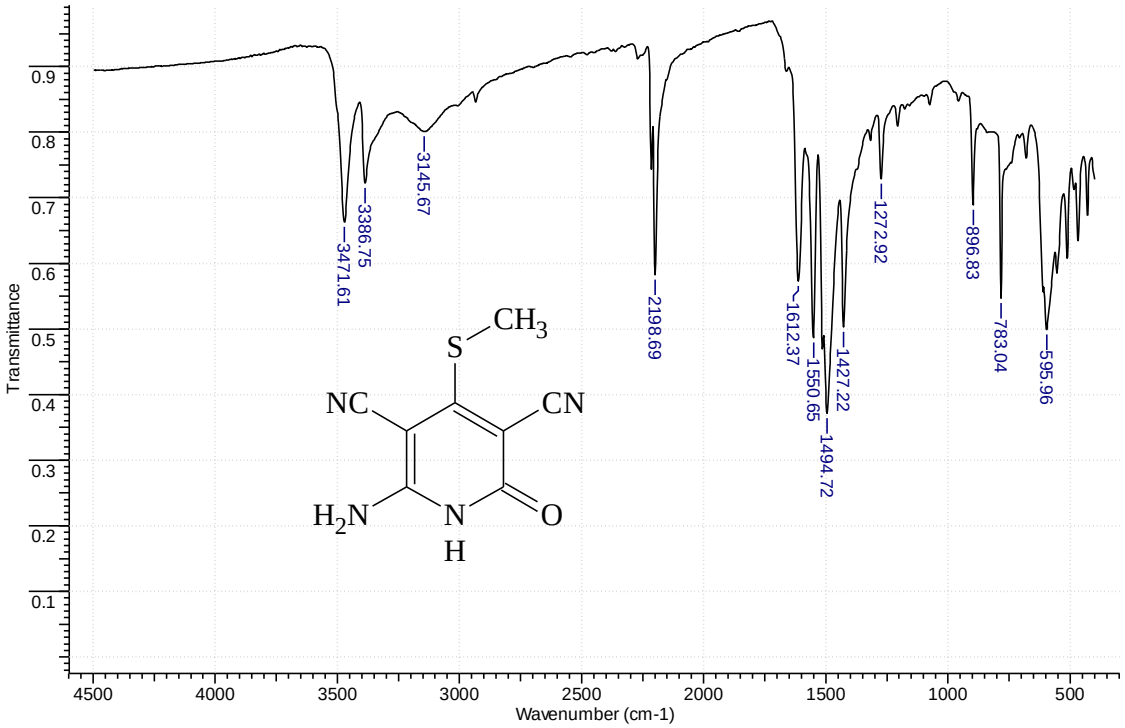
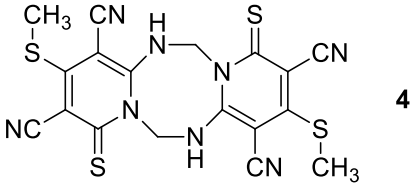


Figure 1. IR spectrum of 6-amino-4-(methylthio)-2-oxo-1,2 dihydropyridine-3,5-dicarbonitrile (**2**; R = CH_3, X = O).

3.2. 3.,10-Bis(methylthio)-1,8-Dithioxo-5,6,12,13-Tetrahydro-1H,8H-Dipyrido[1,2-a;1′,2′-e][1,3,5,7]Tetrazocine-2,4,9,11-Tetracarbonitrile (4, R = CH_3, X = S)



4

A 50 mL beaker was charged with 0.3 g (0.0013 mol) of 4-(methylthio)-6-amino-2-thioxo-1,2-dihydropyridine-3,5-dicarbonitrile (**2**, R = CH_3, X = S) and 30 mL of DMF. The solution was heated to reflux and then triethylamine (0.3 mL, 0.002 mol) was added. After the starting pyridine **2** dissolved completely, 0.53 mL (0.025 mol) of aq. HCHO (33%, *d* 1.1 g/mL) was added and the mixture was heated while stirring for another 2 h. Finally, the solution was poured into water and the precipitated solid was filtered off to give 3,10-bis(methylthio)-1,8-dithioxo-5,6,12,13-tetrahydro-1H,8H-dipyrido[1,2-a;1′,2′-e][1,3,5,7]tetrazocine-2,4,9,11-tetracarbonitrile. The yield was 300 mg (55%), m.p. > 250 °C. IR spectrum (ν, cm^{-1}): 3459, 3344, 3232 (NH); 2195, 2166 (4 CN); 1651 (C=C, C=N); 1288, 1417 (C=S) (Figure 2).

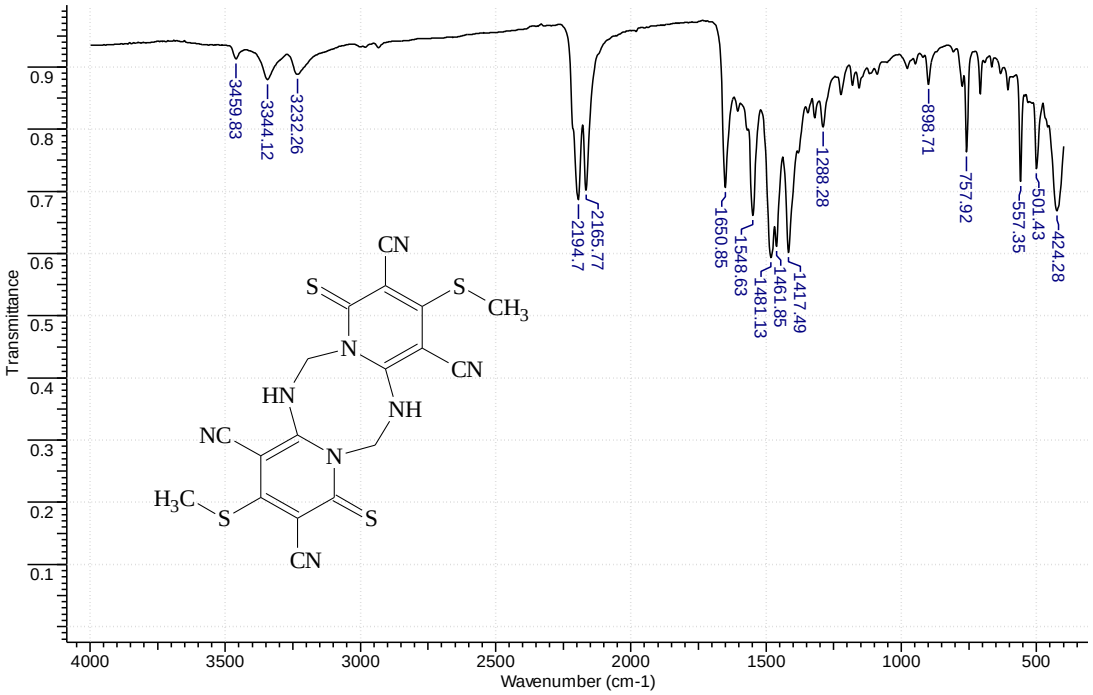


Figure 2. IR spectrum of 3,10-bis(methylthio)-1,8-dithioxo-5,6,12,13-tetrahydro-1H,8H-dipyrido[1,2-a;1′,2′-e][1,3,5,7]tetrazocine-2,4,9,11-tetracarbonitrile (**4**; R = CH_3, X = S).

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