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Proceeding Paper

The Mannich Reaction of the S,N-Binucleophilic Species Derived from Meldrum's Acid with HCHO and Primary Amines †

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Abstract

We investigated the reactivity of a new sulfur-containing compound derived from Meldrum's acid and phenyl isothiocyanate, triethylammonium 1-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)(phenylamino)methanethiolate. Under aminomethylation conditions (using aqueous formaldehyde and primary amines), this compound undergoes a double aminomethylation to form novel 1,3,5-thiadiazine derivatives. These new compounds, 2,2-dimethyl-5-(3-phenyl-1,3,5-thiadiazinan-2-ylidene)-1,3-dioxane-4,6-diones, were previously unknown. This study also explores some properties of the synthesized 1,3,5-thiadiazines.

Keywords: 1,3,5-thiadiazines; mannich reaction; meldrum's acid

1. Introduction

1,3,5-Thiadiazines are an important class of heterocyclic compounds with a wide range of practical uses [1–7]. Among all possible strategies for constructing a 1,3,5-thiadiazine scaffold, one should especially highlight the direction based on various variants of the Mannich reaction–double aminomethylation of various S,N-binucleophilic substrates (thioamides, dithiocarbamates, 2-mercaptoazoles and –azines, thiolactams, etc.), thiomethylation of amines and other N-nucleophiles, etc [1–7]. Due to its efficiency, ease of implementation, and availability of initial reagents, this approach is now perhaps the most popular method among heterocyclist chemists that allows for the production of partially hydrogenated 1,3,5-thiadiazines (or perhydro-1,3,5-thiadiazines) in a single synthetic operation.

It is known from the literature that active methylene compounds, and in particular Meldrum's acid, readily react with heterocumulenes such as isothiocyanates, carbon disulfide etc. to form 1,3-dinucleophilic reagents [8–10]. We decided to study the behavior of the reaction product of Meldrum's acid with phenyl isothiocyanate–triethylammonium 1-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)(phenylamino)-methanethiolate–under the conditions of the aminomethylation reaction. It has been established that the mentioned thiolate reacts by double aminomethylation with aqueous HCHO and primary aliphatic and aromatic amines to form 1,3,5-thiadiazine derivatives-2,2-dimethyl-5-(3-

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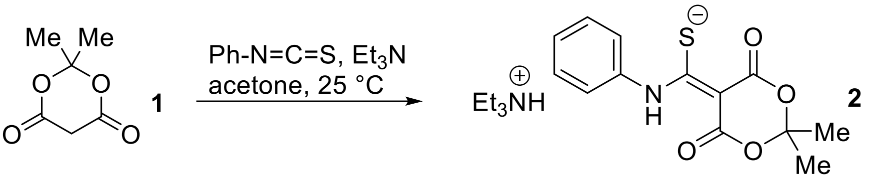
phenyl-1,3,5-thiadiazinan-2-ylidene)-1,3-dioxane-4,6-diones that were not previously described in the literature. The scope and limitations of the reaction as well as the properties of the obtained 1,3,5-thiadiazine derivatives are discussed.

2. Results and Discussion

We have established that the reaction of Meldrum's acid **1** with phenyl isothiocyanate in the presence of triethylamine yields a previously unreported salt: triethylammonium 1-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)(phenylamino)-methanethiolate **2** (Scheme 1).



Scheme 1. XXX.

The structure of compound **2** was confirmed by a combination of spectroscopic methods, including IR and NMR spectroscopy (Figures 1–3).

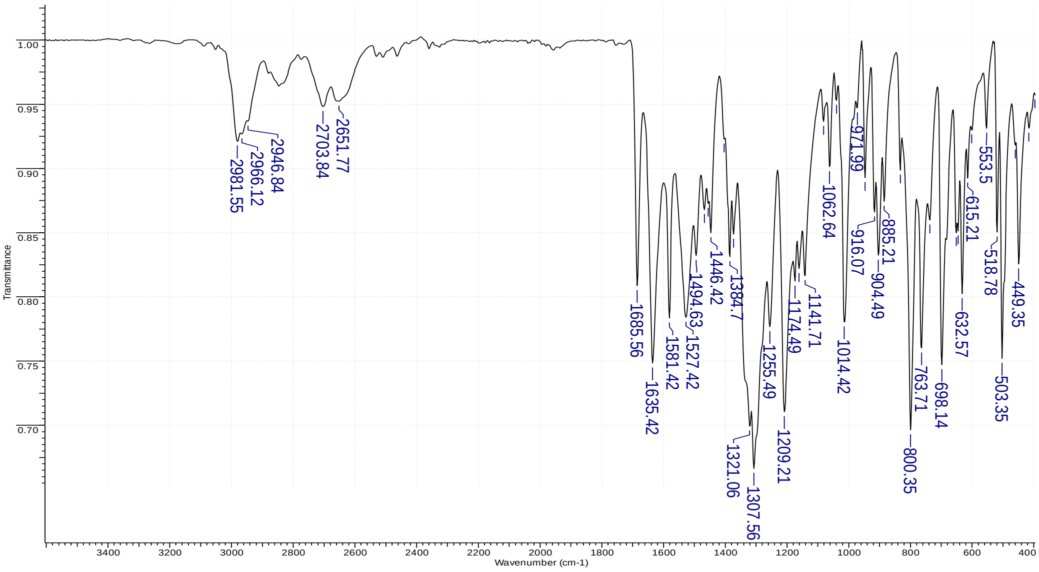


Figure 1. FTIR spectrum (ATR mode) of triethylammonium 1-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)(phenylamino)-methanethiolate **2.**

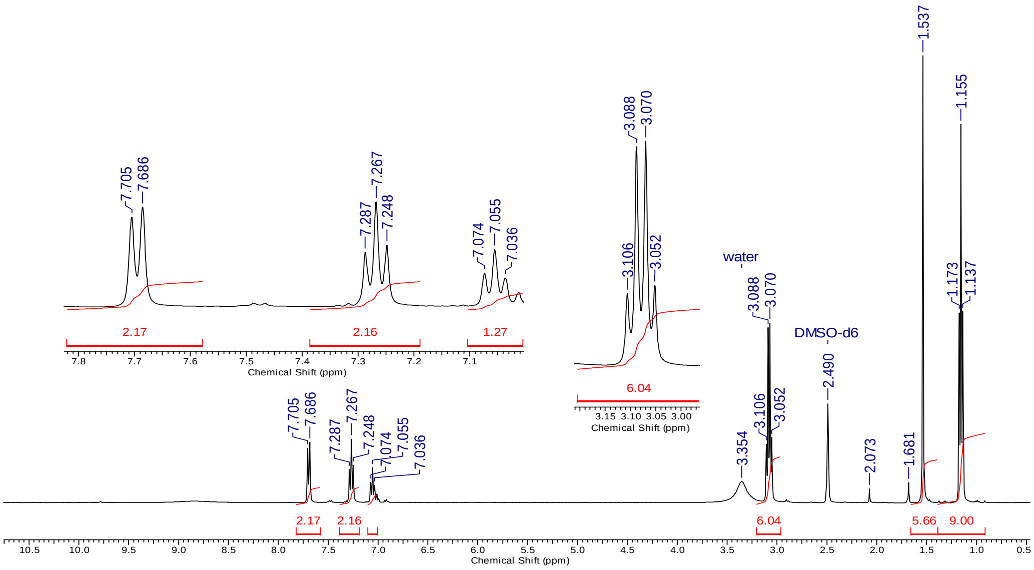


Figure 2. ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of triethylammonium 1-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)(phenylamino)methanethiolate **2.**

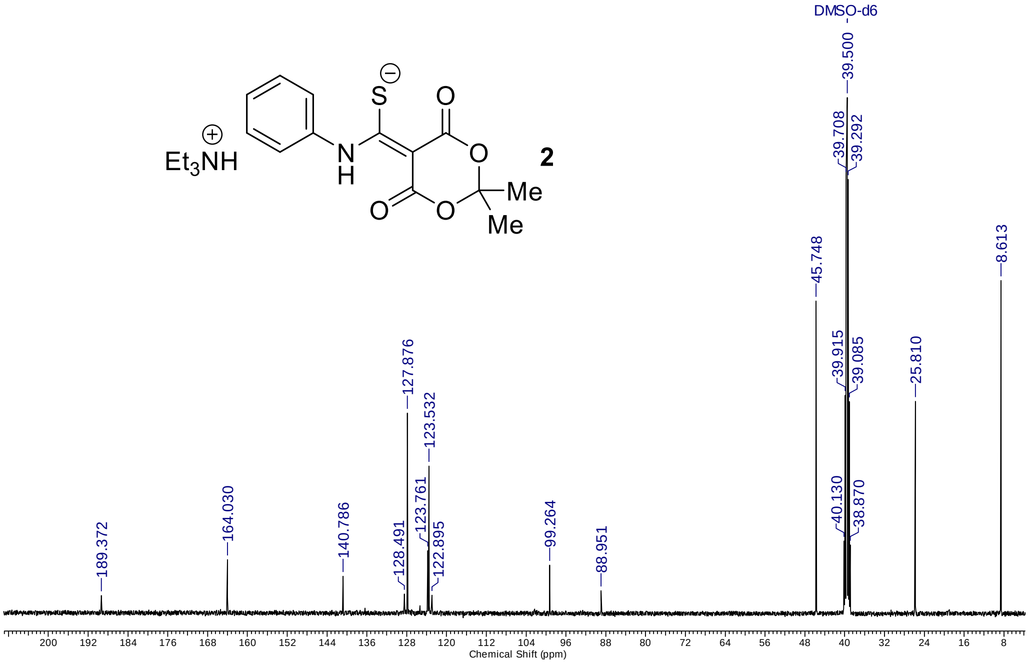
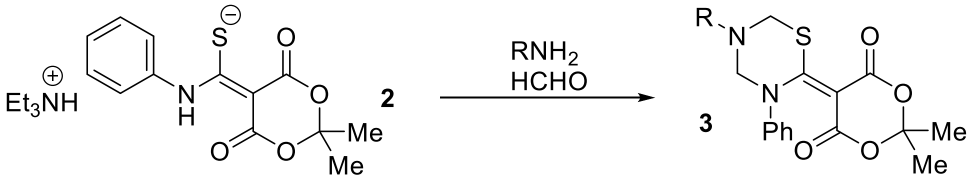


Figure 3. ^{13}C NMR spectrum (101 MHz, DMSO-d_6) of triethylammonium 1-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)(phenylamino)methanethiolate **2.**

We found that thiolates **2** undergo double aminomethylation with aqueous formaldehyde and primary amines to form previously unknown 1,3,5-thiadiazine derivatives **3** (Scheme 2).



Scheme 2. XXX.

To assess the potential biological activity of compounds **2**, **3a** (R= 4-ClC_6H_4), and **3b** (R = 3,4-$Me_2C_6H_3$), we performed in silico predictive analyses using the SwissADME and admetSAR services. The results indicate that thiolate **2** has high gastrointestinal absorption, can cross the blood-brain barrier (BBB), and inhibits the cytochrome P450 isoform CYP2C9. This CYP2C9 inhibitory activity suggests a potential for drug-drug interactions.

In contrast, compounds **3a** and **3b** also exhibit high gastrointestinal absorption but do not penetrate the BBB. Furthermore, they inhibit the CYP2C19, CYP2C9, and CYP3A4 isoforms, while showing no inhibition of CYP2D6 or CYP1A2.

3. Experimental

Synthesis of Triethylammonium (2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene) (phenylamino)methanethiolate (2): Meldrum's acid (2 g, 0.014 mol) was dissolved in acetone (10 mL). Phenyl isothiocyanate (1.7 mL, 0.014 mol) was added to the resulting solution under vigorous stirring. Then triethylamine (2.1 mL, 0.015 mol) was then added dropwise to the mixture; the reaction was exothermic. The mixture was stirred for 4 h at 25 °C, yielding light-yellow crystals. The yield was 4.1 g (77.4%). For analytical purposes, the product was dissolved in a mixture of acetone and ethyl alcohol, and the filtrate was treated with a threefold volume of water.

Synthesis of Compound 3a: Thiolate **2** (0.2 g, 0.5 mmol) was dissolved in ethyl alcohol (5 mL). 4-Chloroaniline (0.1 g, 0.78 mmol) was added to the stirred solution. After the compounds had completely dissolved, aq. 37% HCHO (0.14 mL, 1.87 mmol) was added. The mixture was stirred for 8 h while heating, after which the product was precipitated with an excess of cold water. A white, fine-crystalline powder was obtained with a yield of 0.178 g (78.7%).

Synthesis of Compound 3b: Thiolate **2** (0.2 g, 0.5 mmol) was dissolved in ethyl alcohol (5 mL). Aniline (0.08 g, 0.86 mmol) was added to the stirred solution. After the compounds had completely dissolved, aq. 37% HCHO (0.14 mL, 1.87 mmol) was added. The mixture was stirred for 7 h, after which the product was precipitated with an excess of cold water. A light-yellow powder was obtained with a yield of 0.112 g (50.2%).

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