Synthesis of 6-R-6,7-dihydro-3*H*,5*H*-[1,2,4]dithiazolo[4,3-a][1,3,5]triazine-3-thiones by aminomethylation of xanthane hydride

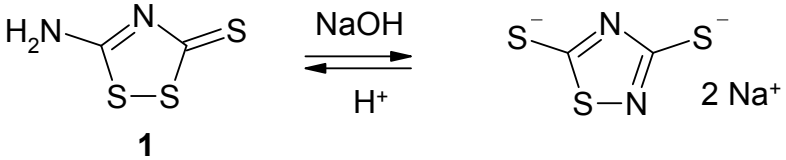
Victor V. Dotsenko[1,2], Tatyana Yu. Evmeshenko[1], Gennady D. Krapivin[3]

[1]*Kuban State University, 149 Stavropolskaya St., Krasnodar 350040, Russian Federation*
[2]*ChemEx Lab, Vladimir Dal' Lugansk National University, Lugansk, 91034 Russian Federation*
[3] *Kuban State Technological University, 2 Moskovskaya st., 350072 Krasnodar, Russian Federation*

Abstract: Xanthane hydride (5-Amino-3*H*-1,2,4-dithiazole-3-thione) reacts with primary amines (1 eq.) and HCHO (2 eq.) under harsh conditions (reflux in DMSO or DMF) to give a hitherto unknown heterocyclic system, 6,7-dihydro-3*H*,5*H*-[1,2,4]dithiazolo[4,3-a][1,3,5]triazine. The products were confirmed by NMR studies.

Keywords: xanthane hydride, Mannich reaction, amnimethylation, NMR studies, dithiazoles, 6,7-dihydro-3*H*,5*H*-[1,2,4]dithiazolo[4,3-a][1,3,5]triazine.

Xanthane hydride (isoperthiocyanic acid, 5-amino-1,2,4-ditiazolin-3-thione **1**) is the very first organic compound obtained by Friedrich Wöhler starting from inorganic predecessors (HCl and mercury thiocyanate) as early as in 1821 [1,2], seven years before the Wöhler's classical synthesis of urea from ammonium cyanate. However, the structure of Xanthane hydride **1** has for a long time remained unclear primarily because of the easy isomerization into perthiocyanic acid (3,5-dimercapto-1,2,4-thiadiazole) derivatives (e.g. upon treatment with strong bases):

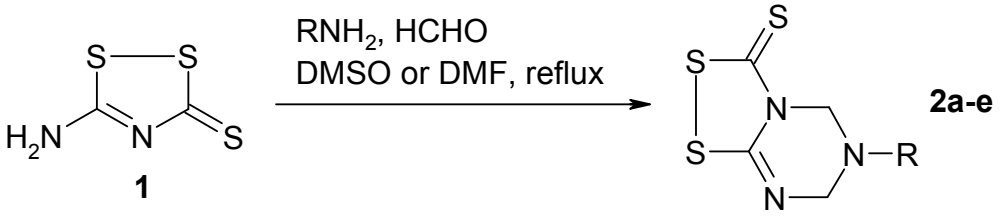


1

The chemistry of xanthane hydride has been reviewed [1,3]. Due to the presence of nucleophilic thioxo- and amino groups, xanthane hydride could be considered as a reactive molecule useful as a starting point for construction of new heterocyclic compounds. However, despite the fact that xanthane hydride is the long-time known and well-studied compound, the reactions leading to the

formation of new heterocyclic systems have been mostly neglected in the literature [1,3]. In the present work we aimed to study the Mannich-type reactions of xanthane hydride **1**.

We found that the aminomethylation of **1** with HCHO and primary amines proceeds under harsh conditions to give previously unknown 6-R-6,7-dihydro-3*H*,5*H*-[1,2,4]dithiazolo[4,3-*a*][1,3,5]triazine-3-thiones **2a-e**.



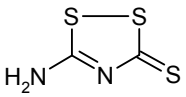
1

2 a R = CH_2Ph; **b** R = Ph; **c** R = 2-MeC_6H_4; **d** R = 2-$MeOC_6H_4$; **e** R = 4-FC_6H_4;

Different approaches to the synthesis of compounds **2a-e** were studied in details. First, we have studied the effect of ratio of reagents on the yields of target products. We were unable to obtain compound **2** in pure form using an excess of HCHO. Upon treatment with excessive HCHO and/or amine, only resinification and clear decomposition were observed.

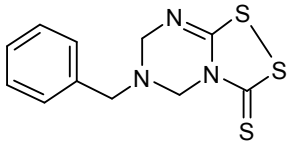
A key factor that led to the success was the use of strictly equivalent amounts of amine and formaldehyde, followed by the addition of an equimolar amount of xanthane hydride. However, when the equivalent amounts of **1**, HCHO and amine were used, the most of **1** remained unchanged and dithiazolotriazines **2** were isolated in low yields (7-23% after purification with flash chromatography). DMF and DMSO were found to be the solvents of choice since no reaction occurs in AcOH, and in EtOH, dioxane or pyridine we failed to obtain any Mannich products due to the difficult solubility of xanthane hydride **1** in these solvents. Further studies to expand the scope of the reaction and optimize the conditions are currently underway and will be published elsewhere.

Experimental

 **1**

The xanthane hydride **1** was obtained according to the modified Wöhler procedure [3,4] as follows: A 200 ml beaker was charged with 35.5 g (0.47 mol) of ammonium thiocyanate dissolved in 50 ml of warm water. Then 100 mL (2.98 mol) of 18% HCl (d = 1.088 g/cm^3) was added dropwise at room temperature. The resulted solid was filtered off and washed with a plenty water to remove NH_4Cl. The yields were 8-12 g (34-51%), yellow needles, mp 200-203 °C.

6-Benzyl-6,7-dihydro-3*H*,5*H*-[1,2,4]dithiazolo[4,3-*a*][1,3,5]triazine-3-thione 2a



Benzylamine (0.25 ml, 0.0024 mol), 21% HCHO aq. solution (0.65ml, 0.0048 mol, d=1.062 g/mL), an appropriate solvent (1.5 mL DMF) and xanthane hydride **1** (0.36 g, 0.0024 mol) were subsequently placed into a 10 mL round bottom flask. The mixture was refluxed until a precipitate formed. The resulting precipitate was filtered off, washed with n-BuOH, and purified by flash chromatography (eluent – hot EtOAc). The yield was 18%, pale yellow crystalline solid. For NMR spectra, see Figures 1 and 2.

IR, ν, cm^{-1}: 2949 (CH_2), 1542 (C=C), 1314 (C=S), 1542 (C=N).

^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 3.87 (s, 2H, CH_2Ph); 4.86 (s, 2H, NCH_2N); 5.17 (s, 2H, NCH_2N); 7.34 (m, 5H, Ph).

^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm: 53.4 (CH_2N); 54.3 (CH_2N); 67.1 ($PhCH_2N$); 127.4 (C-4 Ph); 128.1 (C-2,C-6 Ph); 128.6 (C-3,C-5 Ph); 135.6 (C-1 Ph); 154.3 (C=N); 196.8 (C=S).

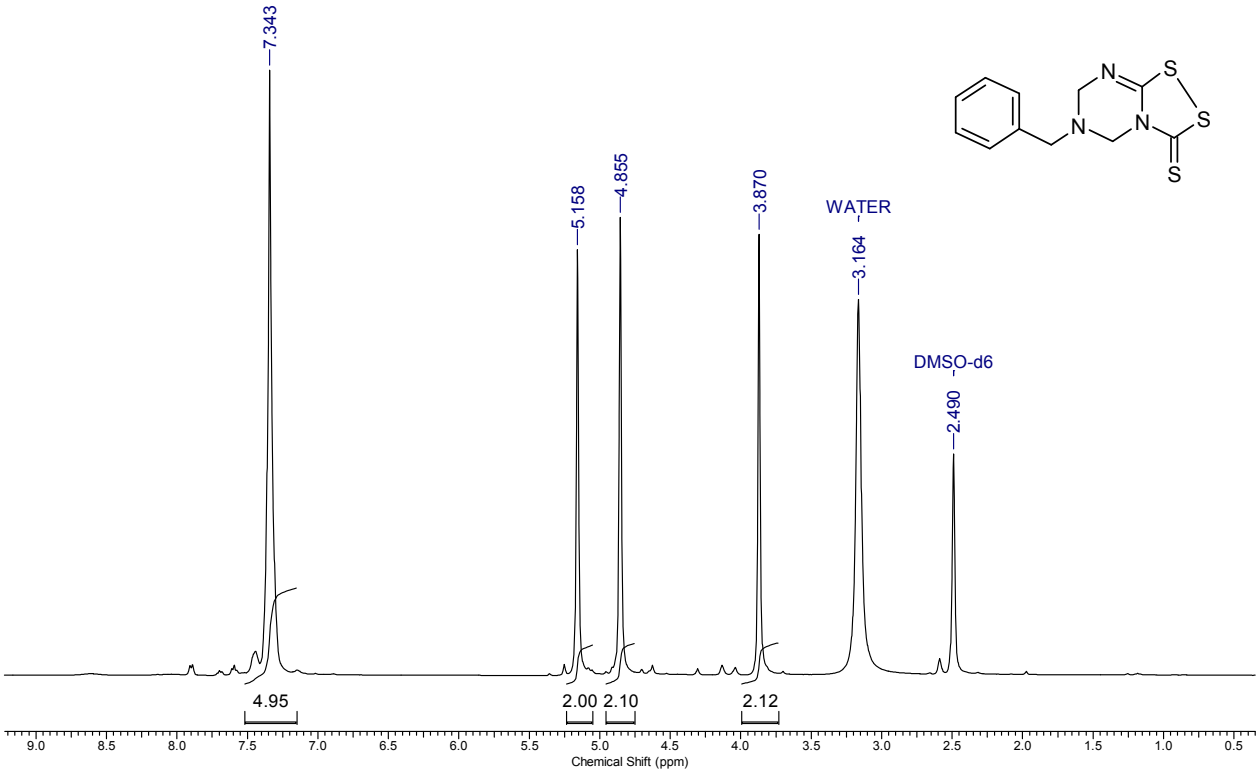


Figure 1. ^{1}H NMR (400 MHz, DMSO-d_6) spectrum of 6-benzyl-6,7-dihydro-3*H*,5*H*-[1,2,4]dithiazolo[4,3-*a*][1,3,5]triazine-3-thione **2a**

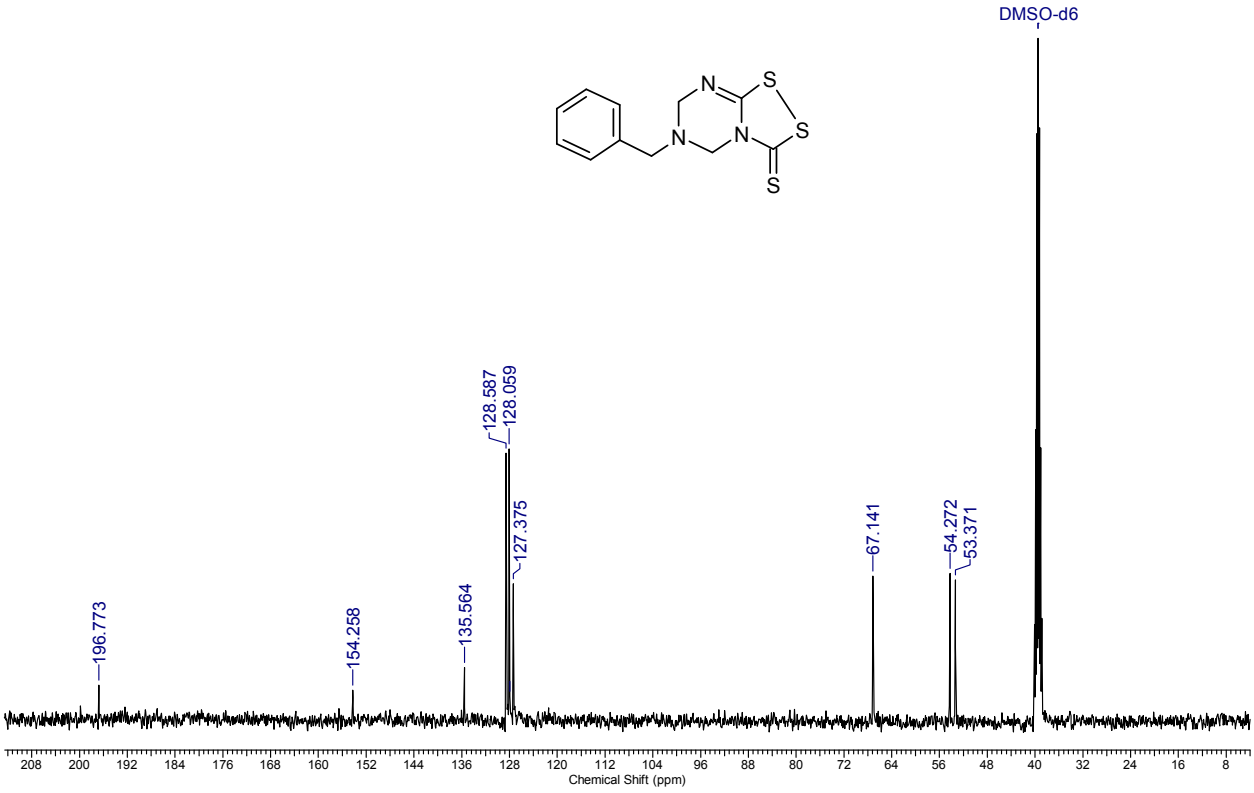


Figure 2. ^{13}C NMR (100 MHz, DMSO-d_6) spectrum of 6-benzyl-6,7-dihydro-3*H*,5*H*-[1,2,4]dithiazolo[4,3-*a*][1,3,5]triazine-3-thione **2a**

In conclusion, we have developed the method for the synthesis of previously unknown [1,2,4]dithiazolo[4,3-*a*][1,3,5]triazines, based on the Mannich-type aminomethylatiion of xanthane hydride with HCHO and primary amines. Further studies on the optimization of the conditions are currently underway.

References

1. A. Z. Rys, D. N. Harpp. Xanthane Hydride / e-EROS Encyclopedia of Reagents for Organic Synthesis. 2008. URL: http://onlinelibrary.wiley.com/doi/10.1002/047084289X.rn00881/abstract
2. C. Glidewell, J. S. McKechnie, P. J. Pogorzelec // J. Chem. Education, 1984, 61 (No 1), pp. 78-79.
3. N. V. Zhorkin, V. A. Ignatov, G. A. Blokh // Voprosy Khim. Khim. Tekhnol. – 1972, № 2. – P. 176-186 (A review on the chemistry of xanthane hydride, in Russian) // Chem. Abstr. 1973, 78, 124470h.
4. Zhang Jinzhong, Zhong Jie, Zhu Deling, Li Baoshan, Shi Mingzhu, Jin Yan, Yin Aijun // Chin JMAP, 2013, Vol. 30, No.3, pp. 299-302 (In Chinese).