chemistry proceedings

MDPI

Proceedings Paper

Synthesis of N-(hydroxymethylene)thioamides by N- hydroxymethylation of 2-cyanothioacrylamides †

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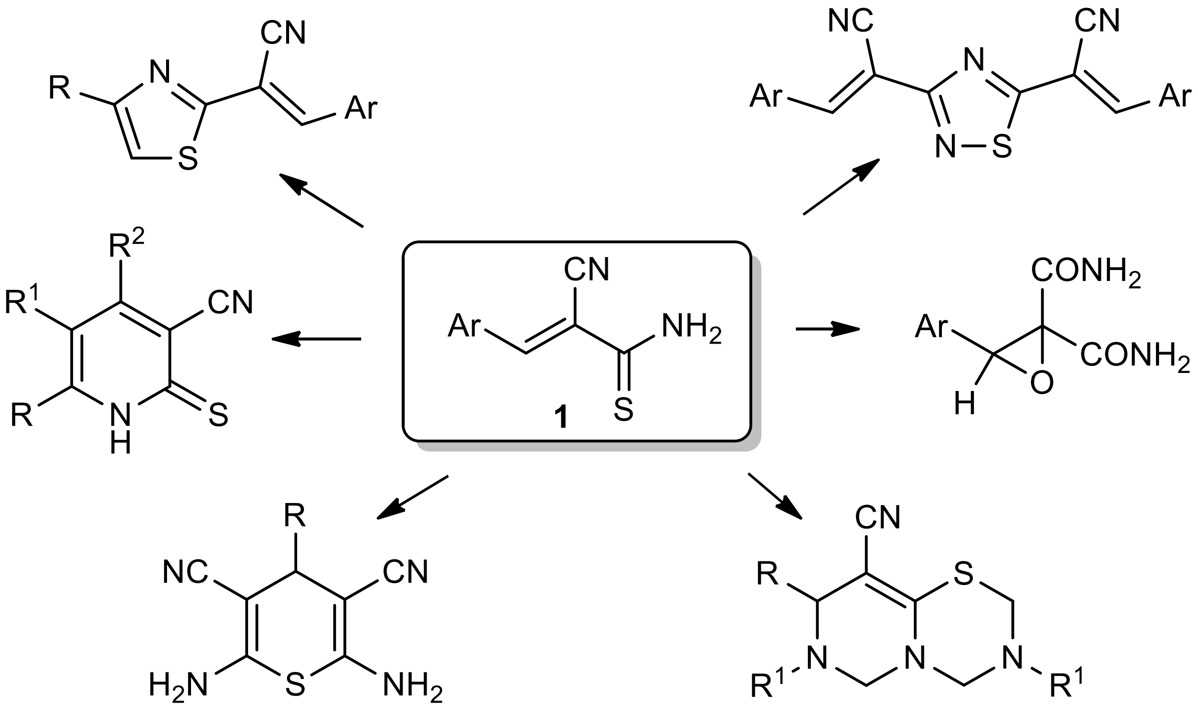
† Presented at the 25th International Electronic Conference on Synthetic Organic Chemistry, 15–30 November 2021; Available online: https://ecsoc-25.sciforum.net/.

Abstract: The condensation products of cyanothioacetamide with aldehydes – (E)-arylmethylenyanothioacetamides – have proven to be readily available and multifunctional starting reagents in the chemistry of S,N-containing compounds. We decided to study the interaction of formaldehyde with thioamides as a possible way to obtain N-(hydroxymethylene)thioamides are promising thioamidoalkylating agents and new ligands for complexation. It was found that the reaction of thioamides and formaldehyde proceeds easily when the reagents are heated in the absence of catalysts in an aqueous-alcohol medium, and leads with good yields to the expected N-(hydroxymethylene)thioamides. Structure of N-(hydroxymethylene)thioamides 2 was confirmed by IR and NMR spectroscopy data.

Keywords: arylmethylenecyanothioacetamides, N-hydroxymethylation

1. Introduction

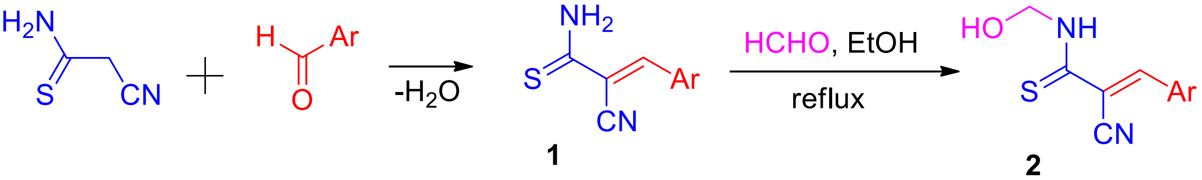
We decided to study the reaction of formaldehyde with thioamides as a possible way to obtain N-(methylol)thioacrylamides - promising thioamidoalkylating agents and new ligands for complexation and possible intermediates in the synthesis of condensed heterocycles of the 1,3,5-thiadiazine series [1-3]. 2-Cyanothioacrylamides 1 (Scheme 1) derived from easily available cyanothioacetamide have recommended themselves as convenient reagents for construction of various S,N-heterocycles [4-7].



Scheme 1. The diversity of compounds prepared from thioacrylamides **1**.

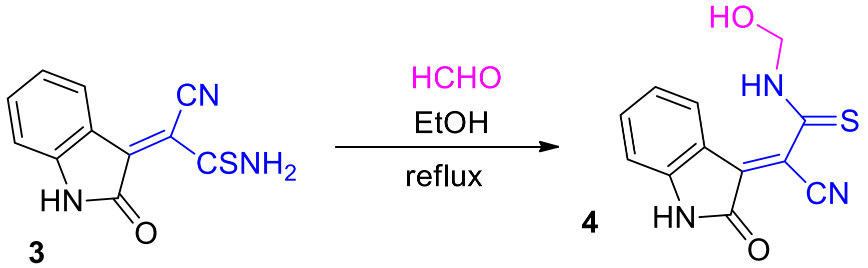
2. Results and discussion

We found that unsaturated thioamides 1 easily react with an excess of aq. 37% formaldehyde when heated in EtOH in the absence of any catalysts with the formation of N-hydroxymethylation products 2 (Scheme 2). N-(Hydroxymethyl)thioamides 2 have a slightly more intense coloration than starting compounds 1. We suggest that moderate yields (46-60%) are due to better solubility in comparison with the starting thioamides 1 in an aqueous alcohol medium, as well as due to side reactions of hydrolysis (retro-Knoevenagel) of starting acrylthioamides 1. The addition of both basic (K2CO3) or acidic (aq. HCl) catalysts leads to resinification of the reaction mass and did not effected the process. The structure of N- (methylol)thioamides 2 was confirmed by IR and NMR spectroscopy data.



Scheme 1. Synthesis and N-hydroxymethylation of thioacrylamides **1**

Next, the condensation product of cyanothioacetamide with isatin – thioacrylamide 3 – reacts with excess of aqueous formalin on heating in EtOH to form product 4 (Scheme 3):



Scheme 3. N-hydroxymethylation of thioacrylamides **3**

The structure of the obtained compounds was confirmed by spectral data. Thus, the IR spectra of the compounds exhibit a characteristic absorption band corresponding to OH stretching vibrations (Fig. 1).

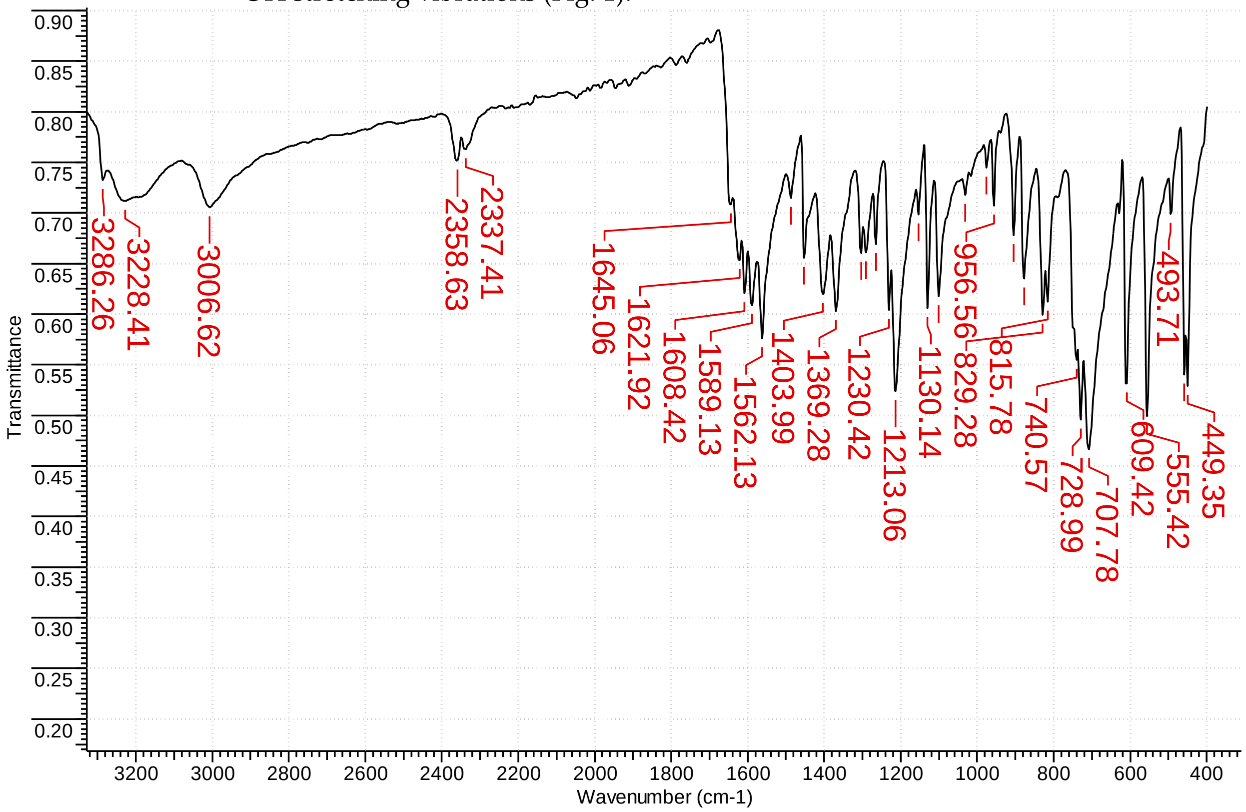
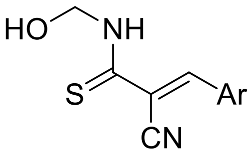


Figure 1. FT-IR (ATR mode) spectrum of compound **4**

3. Experimental

3.1. Method for the synthesis of N-(methylol)thioamides **2**



2

Arylmethylidentianothioacetamide 1 (1.0 mmol) was placed in a beaker, and then 96% ethanol (3-5 ml) and 37% aq. HCHO (5 ml) were added. To dissolve thioamide completely, the mixture was slightly warmed. The reaction mixture was stirred at room temperature for 1-2 h whereas the product precipitated. Over time, the mixture turns a brighter color compared to the starting solutions of thioacrylamides 1. The suspension was kept for 24 hours at 20-25°C, the solid product was filtered off. To remove impurities, the precipitate is recrystallized from acetone or alcohol. The yields are ranging from 40 to 60%.

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