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Proceeding Paper

One-Pot Synthesis of New 4,5,6,7-tetrahydro-3H-[1,2]dithiolo[3,4-b]pyridines Starting from N,N′-Diphenyldithiomalondiamide †

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Abstract: Active methylene compounds such as thioamides are widely used in the organic chemistry for construction of a variety of heterocyclic systems such as thieno[2,3-b]pyridines, 1,2,4-dithiazoles, isothiazoles, 1,2,3-thiadiazoles etc. N,N′-Diphenyldithiomalondiamide (dithiomalondianilide) as compound with methylene active group also is of interest as starting reagent for the synthesis of new N,S-containing heterocycles with potential pharmacological application. However, the reactions of dithiomalondianilide are poorly studied. In the present study we report the synthesis of new 4,5,6,7-tetrahydro[1,2]dithiolo[3,4-b]dithiolopyridine-5-carboxamides through the reaction of dithiomalondianilide with 3-aryl-2-cyanoacrylamides. The products were characterized by means of FTIR and NMR spectroscopy as well as X-ray analysis.

Keywords: [1,2]dithiolo[3,4-b]pyridines; dithiomalonic acid dianilide; active methylene thioamides; dithiolopyridine-5-carboxamides; N,S-containing heterocycles

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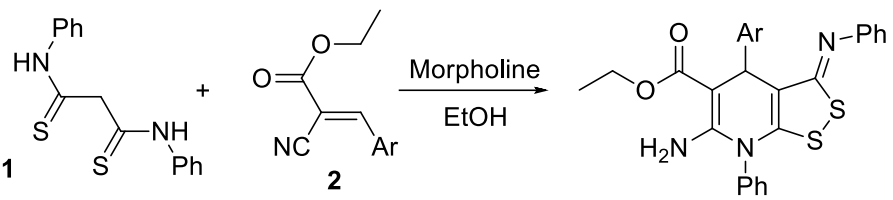
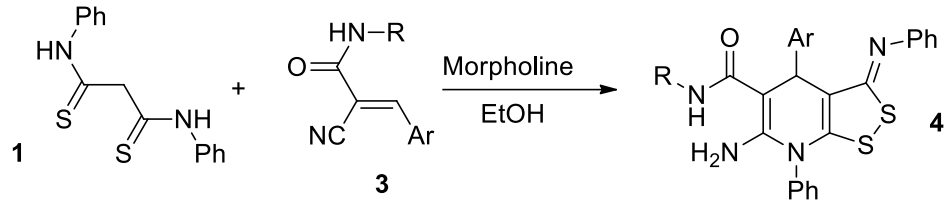
1. Introduction

Active methylene compounds such as thioamides are widely used in the organic chemistry for construction of a variety of heterocyclic systems such as thieno[2,3-b]pyridines [1–4], 1,2,4-dithiazoles [5], isothiazoles [6], 1,2,3-thiadiazoles [7]etc. N,N′-Diphenyldithiomalondiamide (dithiomalondianilide) as compound with methylene active group also is of interest as starting reagent for the synthesis of new N,S-containing heterocycles with potential pharmacological application. However, the reactions of dithiomalondianilide are poorly studied. Thus, up to date only a few reactions with dithiomalondianilide were reported to give heterocyclic compounds. Recently we have reported a new reaction of dithiomalondianilide **1** with 3-aryl-2-cyanoacrylates **2** resulted in the formation of new dithiolodihydropyridines [8]:



Scheme 1. The reaction of N,N′-diphenyldithiomalondiamide with 3-aryl-2-cyano- acrylates.

We suggested that the reaction is applicable to a wide range of Michael acceptors. On our assumptions, the interaction of thioamide **1** with substituted cyanoacrylamides **3** representing substituted acriylonitrile has to lead to the formation of related dithiolodihydropyridine-5-carboxamides **4** according the scheme:

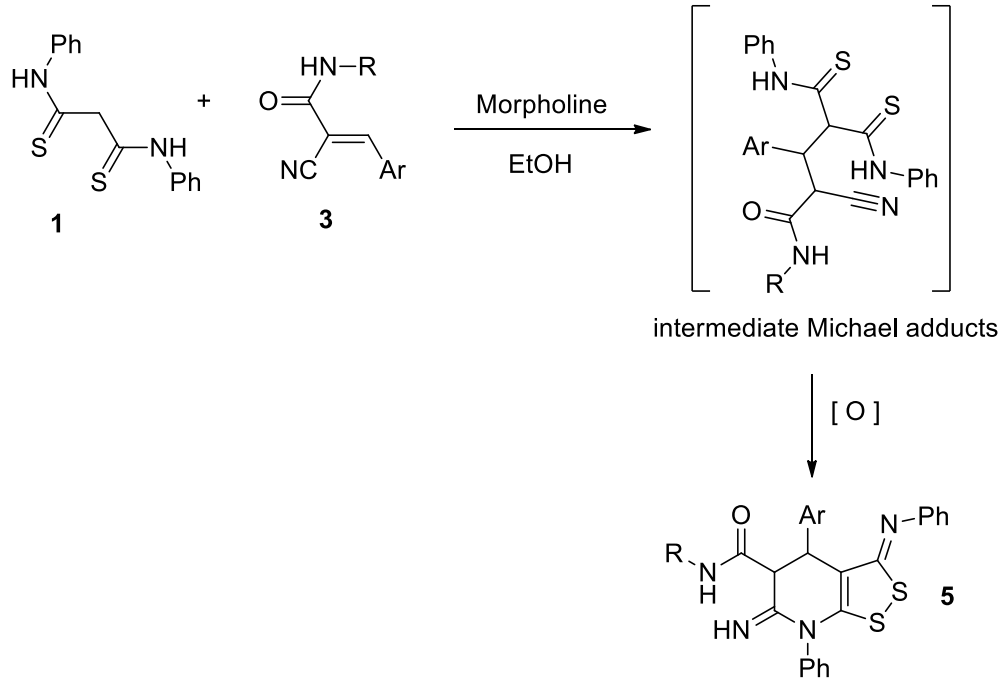


Scheme 2. Expected result of the reaction between dithiomalondianilide with N-substituted 2-cyanoacrylamides.

In general, carboxamides found an application as steel corrosion inhibitors [9], fungicides with a wide antifungal spectrum [10], as antimicrobials, antibacterial and antimalarial drugs [11]. Therefore, the development of new synthetic approaches towards substituted dithiolopyridine-5-carboxamides seems an important and actual task.

2. Result and Discussion

We found that dithiomalondianilide **1** reacts with 3-aryl-2-cyanoacrylamides **3** under mild conditions to afford dithiolotetrahydropyridine-5-carboxamides **5** in good yields. Presumably, the reaction proceeds as the morpholine-catalyzed Michael addition followed by oxidative heterocyclization to give 6-imino-4,5,6,7-tetrahydro-3H-[1,2]dithiolo[3,4-b]pyridine- 5-carboxamides **5** (Scheme 3).



Scheme 3. Preparation of 6-imino-4,5,6,7-tetrahydro-3H-[1,2]dithiolo[3,4-b]pyridine-5-carboxamides **5**.

We previously discovered the crucial role of an oxidant in the successful formation of dithiolopyridine core [8], so the synthesis was carried out under air oxygen. Against our expectations, there was not absorption band of amino group in the IR spectra of prepared compounds. Thus, spectral data indicated the formation of 6-imino-4,5,6,7-

tetrahydro-3H-[1,2]dithiolo[3,4-b]pyridine-5-carboxamides **5** (Figure 1) but not 6-amino-4,7-dihydro-3H- [1,2]dithiolo[3,4-b]pyridine-5-carboxamides **4**.

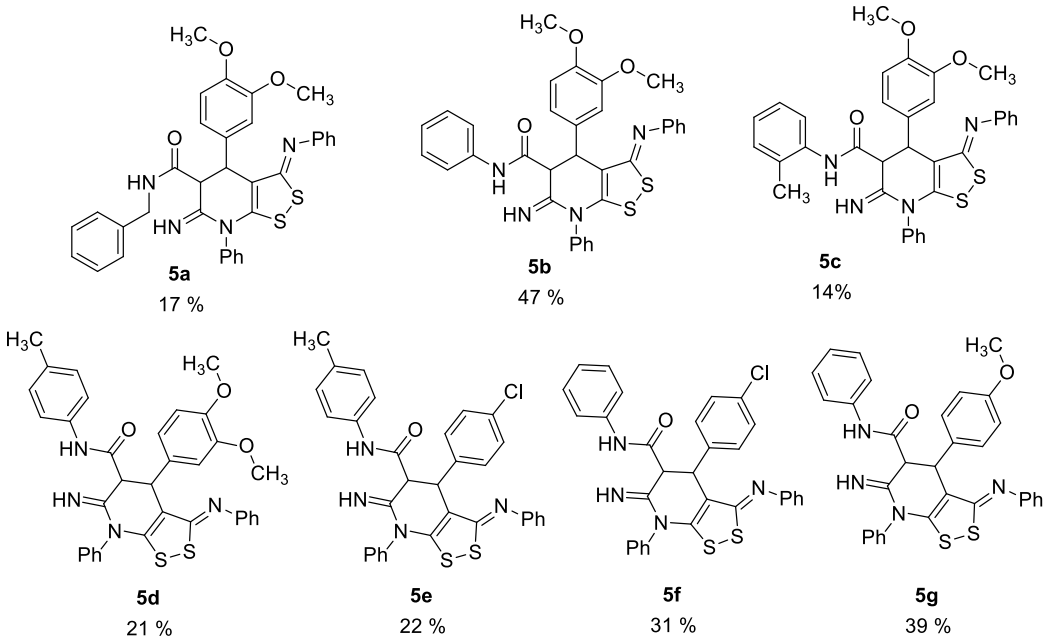
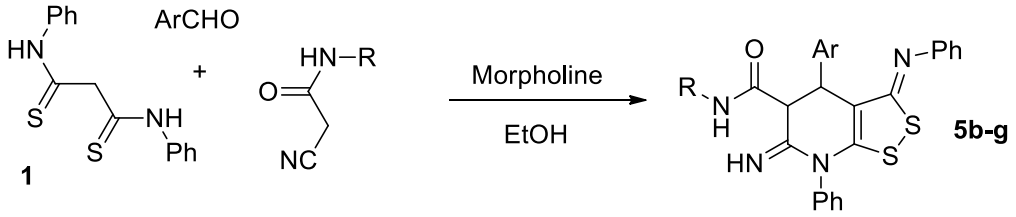


Figure 1. Structures and yields of the prepared 6-imino-4,5,6,7-tetrahydro-3H-[1,2]dithiolo[3,4-b]pyridine-5-carboxamides **5**.

The compounds **5b-g** were also prepared by one-pot method involving the formation of cyanoacrylamide **3** in situ from aromatic aldehydes and N-substituted cyanoacetamide followed by treatment with dithiomalondianilide **1** without isolation of any intermediates (Scheme 4):



Scheme 4. One-pot synthesis of 6-imino-4,5,6,7-tetrahydro-3H-[1,2]dithiolo[3,4-b]pyridine-5-carboxamides **5b-g**.

3. Experimental

*3.1. Procedure for the Preparation of 4,5,6,7-tetrahydro-3H-[1,2]dithiolo[3,4-b]pyridine **5a***

Cyanoacrylamide **3a** (0.9 mmol) and 0.9 mmol of thioamide **1** were suspended in EtOH and an excess of morpholine (1.5 mmol) was added. The reaction mixture then was refluxed until thioamide **1** was completely consumed. The reaction was monitored by TLC. Yellow crystalline precipitate was filtered off, washed with ethanol to give [1,2]dithiolo[3,4-b]pyridine **5a**.

*3.2. Procedure for One-Pot Preparation of 4,5,6,7-tetrahydro-3H-[1,2]dithiolo[3,4-b]pyridines **5b-g***

An aromatic aldehyde (1.5 mmol) and corresponding N-substituted cyanoacetamide (1.5 mmol) were dissolved in ethanol (10 mL), and an excess of morpholine (10 mmol) was added. The reaction mixture was heated until cyanoacetamide was consumed completely. Then an equimolar amount of thioamide **1** was added, and the heating was continued

until cyanoacrylamide intermediate was exhausted. The crystalline precipitate was filtered off, washed with ethanol and recrystallized from ethylacetate.

4. Conclusions

Here we report the first example of the synthesis of dithiolotetrahydropyridine-5-carboxamides through the reaction of dithiomalondianilide with N-substituted 3-aryl-2-cyanoacrylamides. A series of new dithiolotetrapyridines was prepared in modest yields (17–47%).

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