

Proceeding Paper

One-Pot Synthesis of New 4,5,6,7-tetrahydro-3H-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 the 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 a compound with methylene active group is also of interest as a 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*]dithiopyridine-5-carboxamides through the reaction of dithiomalondianilide with 3-aryl-2-cyanoacrylamides. The products were characterized using FTIR and NMR spectroscopy as well as X-ray analysis.

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



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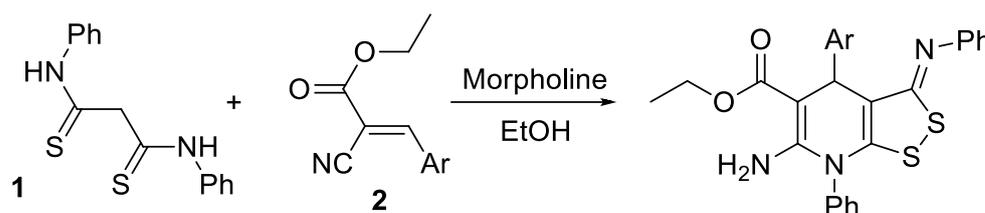
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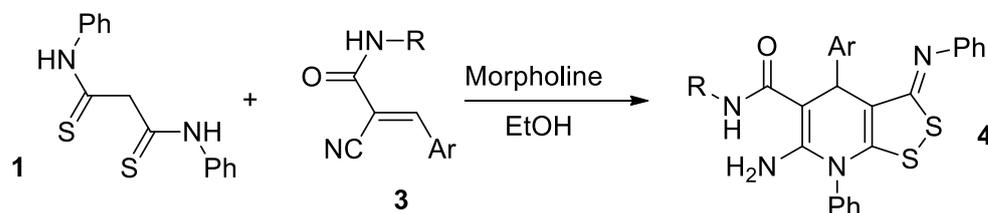
1. Introduction

Active methylene compounds such as thioamides are widely used in organic chemistry for the 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 a compound with a methylene active group is also of interest as a starting reagent for the synthesis of new *N,S*-containing heterocycles with potential pharmacological applications. However, the reactions of dithiomalondianilide are poorly studied. Thus, up to date, only a few reactions with dithiomalondianilide have been reported to give heterocyclic compounds. Recently, we reported a new reaction of dithiomalondianilide **1** with 3-aryl-2-cyanoacrylates **2** that resulted in the formation of new dithiolodihydropyridines [8] (Scheme 1):



Scheme 1. The reaction of *N,N'*-diphenyldithiomalondiamide with 3-aryl-2-cyanoacrylates.

We suggested that the reaction is applicable to a wide range of Michael acceptors. Our assumption is that the interaction of thioamide **1** with substituted cyanoacrylamides **3** representing substituted acrylonitrile has to lead to the formation of related dithiolodihydropyridine-5-carboxamides **4**, according the Scheme 2:

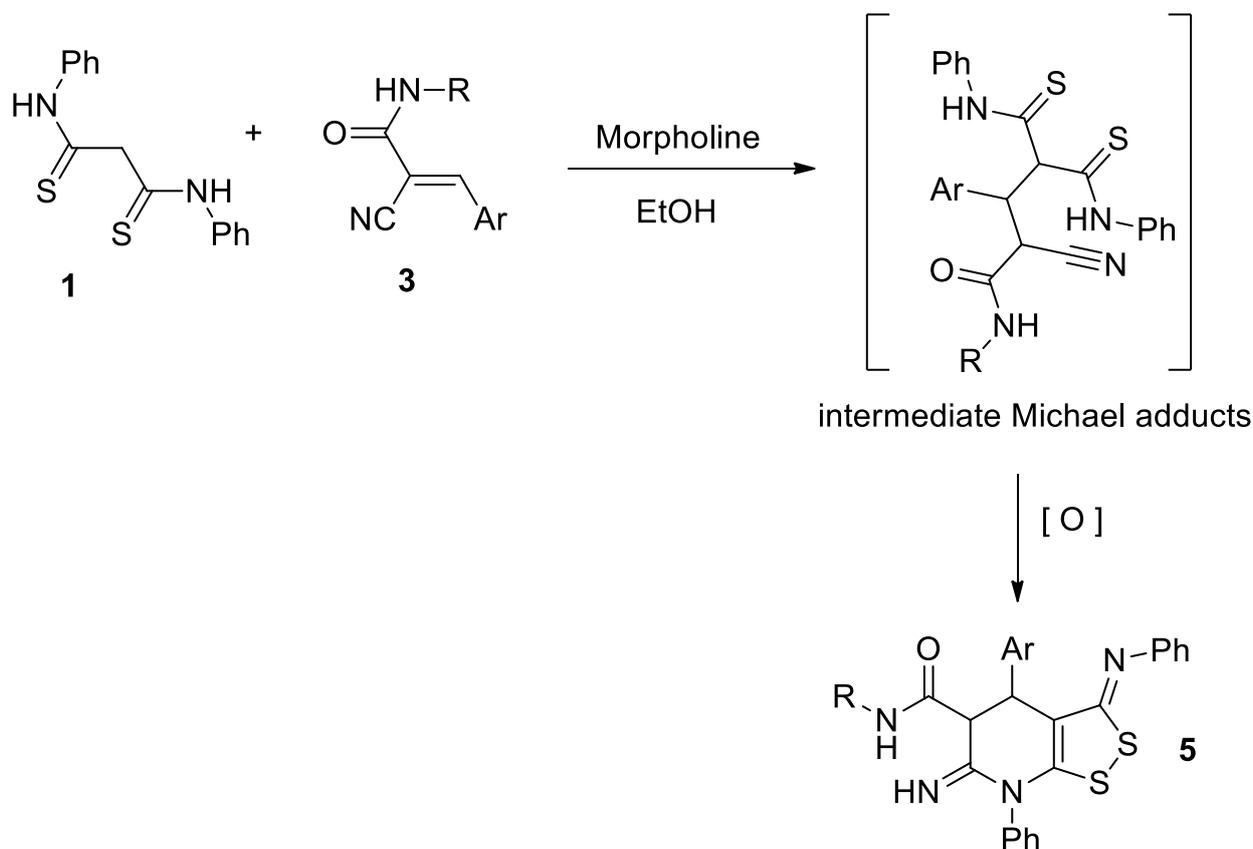


Scheme 2. Expected result of the reaction between dithiomalondianilide with N-substituted 2-cyanoacrylamides.

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

2. Result and Discussion

We found that dithiomalondianilide **1** reacts with 3-aryl-2-cyanoacrylamides **3** under mild conditions to create dithiolotetrahydropyridine-5-carboxamides **5** in good yields. Presumably, the reaction proceeds as the morpholine-catalyzed Michael addition is 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 dithiopyridine core [8], so the synthesis was carried out under air oxygen. Against our expectations, there was no absorption band of amino group in the IR spectra of prepared compounds. Thus, the 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**.

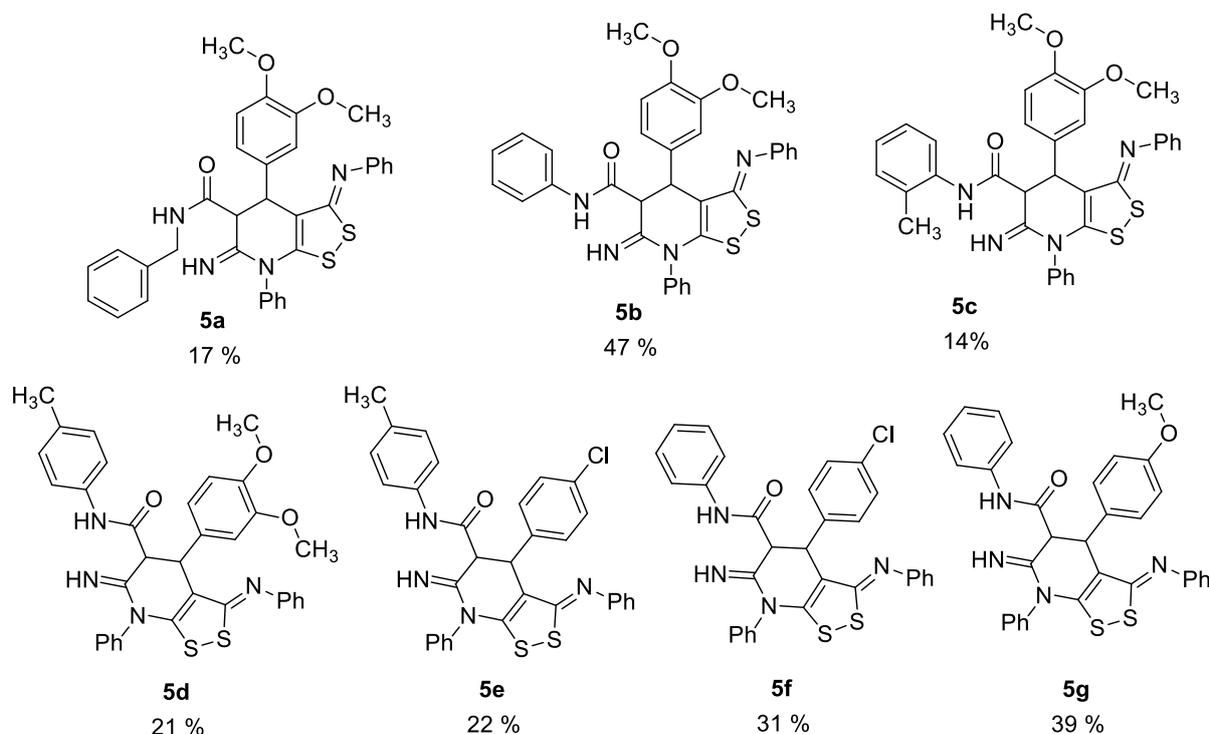
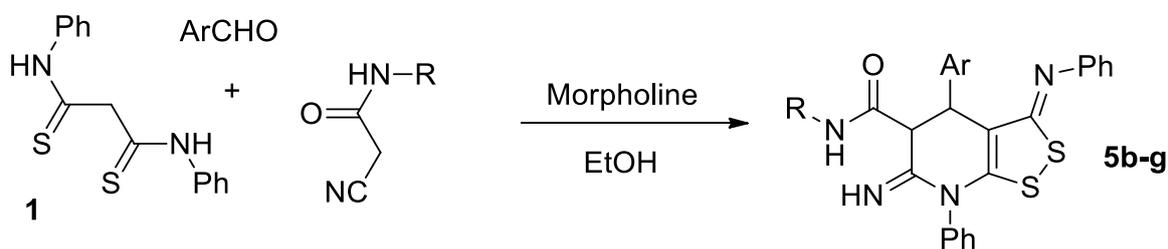


Figure 1. Structures and yields of the prepared 6-imino-4,5,6,7-tetrahydro-3H-[1,2]dithiolo[3,4-b]pyridine-5-carboxamides **5**.

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 was then 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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References

1. Dotsenko, V.V.; Buryi, D.S.; Lukina, D.Y.; Krivokolysko, S.G. Recent advances in the chemistry of thieno[2,3-b]pyridines 1. Methods of synthesis of thieno[2,3-b]pyridines. *Russ. Chem. Bull. Int. Ed.* **2020**, *69*, 1829–1858. [[CrossRef](#)]
2. Bakhite, E.A.-G. Recent trends in the chemistry of thienopyridines. *Phosphorus Sulfur Silicon Relat. Elem.* **2003**, *178*, 929–992. [[CrossRef](#)]
3. Litvinov, V.P.; Dotsenko, V.V.; Krivokolysko, S.G. The chemistry of thienopyridines. *Adv. Heterocycl. Chem.* **2007**, *93*, 117–178.
4. Sajadikhah, S.S.; Marandi, G. Recent approaches to the synthesis of thieno[2,3-b]pyridines (microreview). *Chem. Heterocycl. Compd.* **2019**, *55*, 1171–1173. [[CrossRef](#)]
5. Metwally, M.A.; Abdel-Latif, E.; Bondock, S. Thiocarbamoyl derivatives as synthons in heterocyclic synthesis. *J. Sulfur Chem.* **2007**, *28*, 431–466. [[CrossRef](#)]
6. Taubert, K.; Kraus, S.; Schulze, B. Isothiazol-3(2H)-Ones, Part I: Synthesis, reactions and biological activity. *J. Sulfur Chem.* **2002**, *23*, 79–121. [[CrossRef](#)]
7. Shafran, Y.; Glukhareva, T.; Dehaen, W.; Bakulev, V. Recent developments in the chemistry of 1,2,3-thiadiazoles. *Adv. Heterocycl. Chem.* **2018**, *126*, 109–172.
8. Dotsenko, V.V.; Sinotsko, A.E.; Strelkov, V.D.; Varzieva, E.A.; Russkikh, A.A.; Levchenko, A.G.; Temerdashev, A.Z.; Aksenov, N.A.; Aksenova, I.V. Alkyl 4-Aryl-6-amino-7-phenyl-3-(phenylimino)-4,7-dihydro-3H-[1,2]dithiolo[3,4-b]pyridine-5-carboxylates: Synthesis and Agrochemical Studies. *Molecules* **2023**, *28*, 609. [[CrossRef](#)] [[PubMed](#)]
9. Erami, R.S.; Amirnasr, M.; Meghdadi, S.; Talebian, M.; Farrokhpour, H.; Raeissi, K. Carboxamide derivatives as new corrosion inhibitors for mild steel protection in hydrochloric acid solution. *Corros. Sci.* **2019**, *151*, 190–197. [[CrossRef](#)]
10. Luo, B.; Ning, Y. Comprehensive overview of carboxamide derivatives as succinate dehydrogenase inhibitors. *J. Agric. Food Chem.* **2022**, *70*, 957–975. [[CrossRef](#)] [[PubMed](#)]
11. Kaya, M.; Demir, E.; Bekci, H. Synthesis, characterization and antimicrobial activity of novel xanthene sulfonamide and carboxamide derivatives. *J. Enzym. Inhib. Med. Chem.* **2013**, *28*, 885–893. [[CrossRef](#)] [[PubMed](#)]

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