chemistry proceedings

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Proceedings

N-(Thieno[2,3-b]Pyridin-3-yl)Cyanoacetamides: Synthesis and Cyclizations †

Tatyana S. Didikina [1], Elena A. Chigorina [2], Darya Yu. Lukina [1], Alexander V. Bespalov [1], Victor V. Dotsenko [1,3,*] and Nicolai A. Aksenov [3]

[1] Kuban State University, 149 Stavropolskaya str, Krasnodar 350040, Russia;
[2] The Federal State Unitary Enterprise "Institute of Chemical Reagents and High Purity Chemical Substances" of National Research Centre "Kurchatov Institute", 3 Bogorodsky Val, Moscow 107076, Russia;
[3] Department of Chemistry, North Caucasus Federal University, 1a Pushkin St., 355009 Stavropol, Russia;
* Correspondence: victor_dotsenko@bigmir.net
† Presented at the 24th International Electronic Conference on Synthetic Organic Chemistry, 15 November–15 December 2020; Available online: https://ecsoc-24.sciforum.net/.

Abstract: A series of N-(thieno[2,3-b]pyridin-3-yl)cyanoacetamides were prepared by reaction of 3-aminothieno[2,3-b]pyridines with 1-cyanoacetyl-3,5-dimethytlpyrazole. Upon treatment with alkali, N-(2-alkoxycarbonylthieno[2,3-b]pyridin-3-yl)cyanoacetamides undergo Camps-type cyclization to give dipyridothiophenes. The relative stability of their tautomers was estimated by quantum chemical calculations. In contrast, cyclization of 3-(2-cyanoacetamido)thieno[2,3-b]pyridine-2-carboxamides lead to the formation of pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidines.

Keywords: heterocyclization; Camps reaction; thienopyridines; cyanoacetylation

1. Introduction

Cyanoacetamides belong to the most popular building blocks in organic synthesis (for reviews, see [1–6]). A number of cyanoacetylation reactions are known and plenty of methods have been reported. The most efficient methods include direct cyanoacetylation of molecules using acylating agents such as cyanoacetyl chloride, cyanoacetic acid + dimethylaminopyridine + DCC (N,N′-dicyclohexylcarbo-dimide), cyanoacetic acid + acetic anhydride [4], and 1-(cyanoacetyl)-3,5-dimethylpyrazole **1** [7]. 1-(Cyanoacetyl)-3,5-dimethylpyrazole **1** is very cheap, handy and preparatively easily accessible from acetylacetone and cyanoacethydrazide. It was suggested as a better alternative to most of the cyanoacetylating agents in reactions with nitrogen nucleophiles and for various heterocyclization processes [8–12]. Pyrazole **1** reacts with a variety of amines, including heterocyclic amines [7]. However, the reactions with 3-aminothieno[2,3-b]pyridines have not been reported so far prior to our studies. 3-Aminothieno[2,3-b]pyridines bear privileged thienopyridine scaffold and belong to a popular class of compounds with a very broad spectrum of biological activity [13–15]. The chemistry of 3-aminothieno[2,3-b]pyridines have been reviewed [16–20].

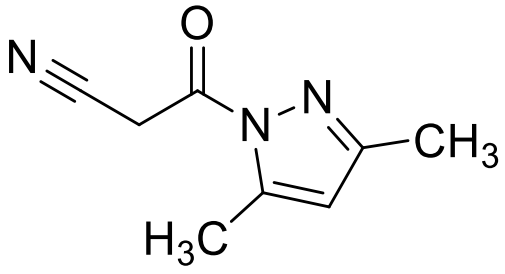

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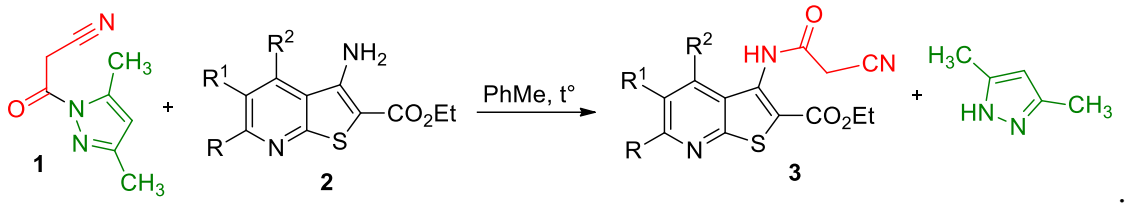
Figure 1. The structure of 1-(cyanoacetyl)-3,5-dimethylpyrazole **1**.

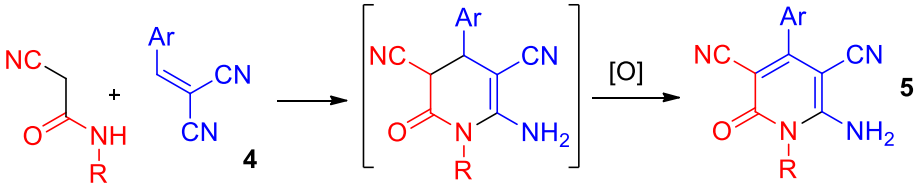
2. Results and Discussion

We found that thienopyridines **2** readily reacted with 1-(cyanoacetyl)-3,5-dimethylpyrazole **1** to give new substituted cyanoacetamides **3** in good yields (Scheme 1).



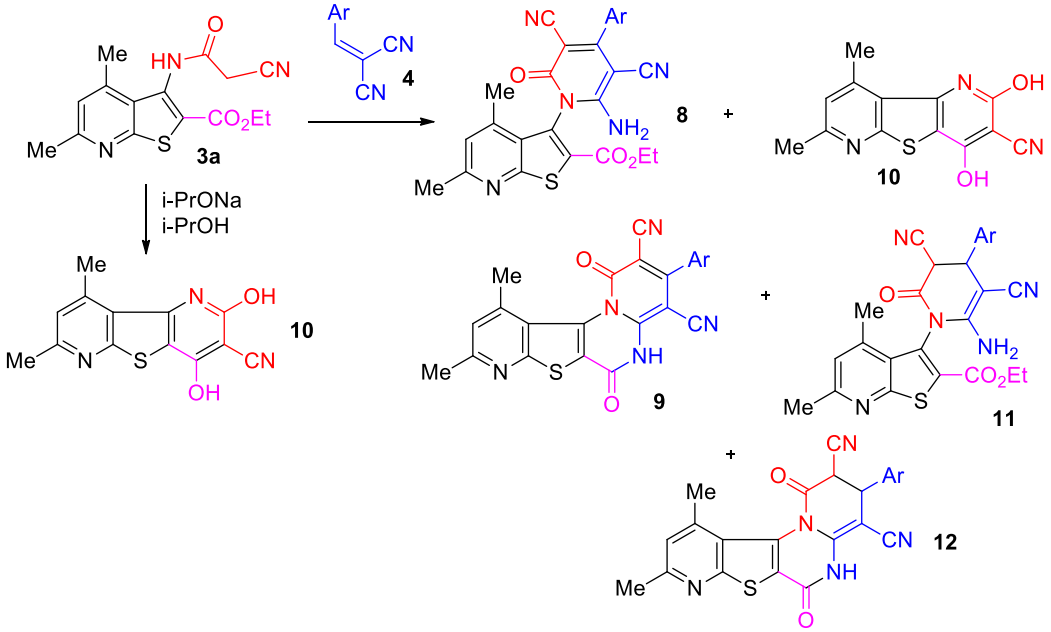
Scheme 1. Reaction of cyanoacetylpyrazole **1** with thienopyridines **2**.

Taking into account the synthetic potential of cyanoacetamides [1,2,4], we decided to study reactions of **3** with 2-(arylmethylidene)malononitriles **4**. In general, cyanoacetamides are known to react with arylmethylidene malononitriles **4** to afford pyridines **5** (Scheme 2) [1,4].



Scheme 2. Reaction of cyanoacetamides with arylmethylidene malononitriles **4**.

We studied the reaction of 3-(cyanoacetylamino)thienopyridines **3** with arylmethylidene malononitriles **4**. Regardless of the base catalyst used (morpholine or potassium hydroxide), compounds **3** reacted with **4** in a non-selective manner to give mixtures of compounds 8–12 at different ratios, which we failed to separate (Scheme 3). The products were identified by HPLC/MS and ^{1}H NMR. Compound **10** was formed *via* competing intramolecular Camps-type cyclization of the starting thienopyridine substrate (Scheme 3).



Scheme 3. Reaction of cyanoacetamides **3** with arylmethylidene malononitriles **4**.

Compound **10** can exist as a few tautomers **10A–10D** (Fig.1). Since it is hard to determine unambiguously the tautomer structure on the basis of NMR and IR data, the relative stability of tautomers was estimated by quantum chemical calculations.

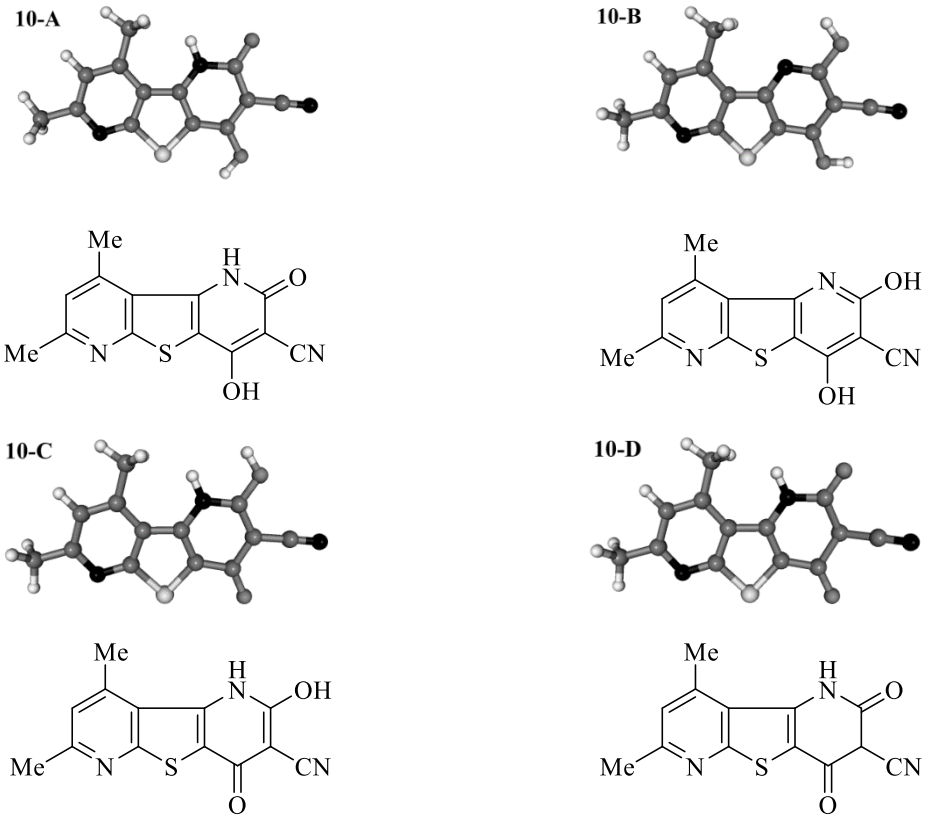
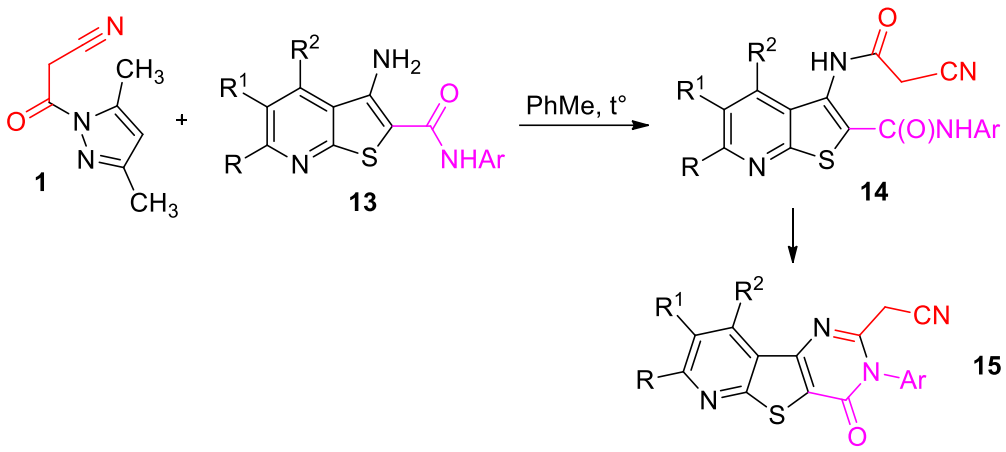


Figure 1. Suggested tautomers for structure **10.**

The calculations were performed using density functional theory with the B3LYP hybrid functional (Becke exchange functional and Lee-Yang-Parr correlation functional) and 6-31G(d,p) split-valence basis set using GAMESS software package. The obtained structures were visualized using Molekel. The ground state energies were calculated with preliminary geometry optimization with a similar basis set. Nonspecific solvation of tautomers in DMSO was taken into account in terms of the conducting polarizable continuum model (CPCM). The most stable tautomer in the gas phase is **10B**, and the energy of tautomer **10A** is higher by 25.8 kJ/mol. Noteworthy that different results were obtained by PCM for DMSO. In this case, the most stable was tautomer **10A**, though the energy difference between **10A** and **10B** was as small as 5.2 kJ/mol. These results allowed us to presume that compound **10** in the crystalline state has structure **10B** which can be converted to tautomer 10A upon dissolution in DMSO, since the latter is solvated more effectively. The strongest solvation by DMSO was predicted for tautomer **10C**; however, its energy still remains relatively high (the difference is 20.2 kJ/mol relative to **10A**). Structure **10D** is the least favorable both in the gas phase and in DMSO solution and seems therefore hardly probable.

Finally, we studied the reactions of thienopyridine-2-carboxamides **13** with 1-(cyanoacetyl)-3,5-dimethylpyrazole **1**. As for thienipyridines **2**, the products were corresponding cyanoacetamides **14**.However, the cyclization of **13** proceeds in quite different way and afford pyridothienopyrimidines **15**.



Scheme 4. Reaction of cyanoacetylpyrazole **1** with thienopyridines **13**.

3. Experimental

Preparation of 3-[(cyanoacetyl)amino]thieno[2,3-b]pyridine-2-carboxylates 3. General Procedure

A hot solution of 15 mmol of thienopyridine **2** in 25-30 mL of anhydrous toluene was added dropwise to a solution of 3.00 g (18.4 mmol) of fr4eshly prepared and dried 1-(cyanoacetyl)-3,5-dimethylpyrazole **1** in 10 mL of anhydrous toluene. The resulting solution was refluxed for 5 h (TLC); after ~20 min, the product began to precipitate. The mixture was cooled, and the white solid was filtered off, washed with toluene and ethanol, and dried.

Ethyl 3-[(cyanoacetyl)amino]-4,6-dimethylthieno[2,3-b]pyridine-2-carboxylate (**3a**). Yield 71%, colorless crystals pourly soluble in acetone and insoluble in boiling ethanol. An analytical sample was obtained by recrystallization from ethanol–acetic acid (1 : 3). IR spectrum, ν, cm^{-1}: 3240 br (N–H), 2250 w (C≡N), 1715 s and 1670 s (C=O). ^{1}H NMR spectrum, δ, ppm: 1.31 t (3H, CH_2CH_3, ^3J = 6.9 Hz), 2.55 s (3H, CH_3), 2.58 s (3H, CH_3), 3.96 s (2H, CH_2CN), 4.31 q (2H, OCH_2, ^3J = 6.9 Hz), 7.19 s (1H, 5-H), 10.35 s (1H, NH).

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