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Synthesis of New Nicotinamides Starting from Monothiomalonanilide †

Victor V. Dotsenko [1,2,*], Radmila N. Gornichenko [1], Ilya O. Kurochkin [1] and Nicolai A. Aksenov [2]

[1] Department of Organic Chemistry and Technologies, Kuban State University, Krasnodar 350040, Russia; radmilagornicenko@gmail.com (R.N.G.); ikurockin785@gmail.com (I.O.K.)
[2] Department of Organic Chemistry, North Caucasus Federal University, Stavropol 355029, Russia; radioanimation@rambler.ru
* Correspondence: victor_dotsenko_@mail.ru
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Abstract

It is known that thioamides containing hydrogen atoms in the α-position of the thiocarbamoyl group exhibit a CH-acidic character. The purpose of the work: synthesis of new nicotinamide derivatives based on monothiomalondianilide and investigation of their properties. According to the known method, we synthesized the initial monothiomalondianilide starting from phenyl isothiocyanate and acetylacetone. The reaction of monothiomalondianilide with arylidenemalonitriles, available by the Knoevenagel reaction, or with aromatic aldehydes and malonitrile in the presence of a base leads to the formation of cyclic Michael adducts—nicotinamide derivatives. New compounds have been studied spectrally (FTIR, NMR ^{1}H, ^{13}C).

Keywords: thioamides; active methylene compounds; nicotinonitriles; nicotinamides

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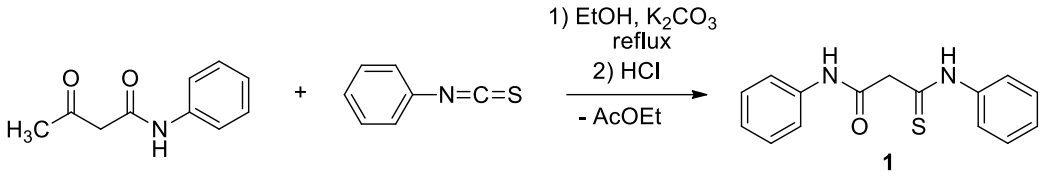
1. Introduction

The chemistry of thioamides containing hydrogen atoms in the α-position to the thiocarbamoyl group represents a promising area of modern organic synthesis, owing to their considerable synthetic potential and the valuable practical properties of the obtained products [1]. Despite its multifunctional nature and obvious potential for diverse transformations, the reactions of monothiomalondianilide **1** remain insufficiently explored. Only a few papers were reported to date dealing with the chemistry of monothiomalondianilide **1** [2–7]. We therefore set out to investigate some new reactions.

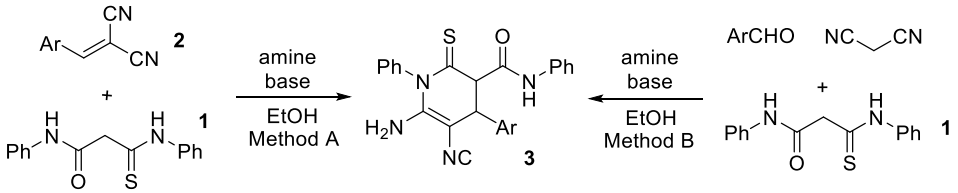
2. Results and Discussion

Using a reported procedure [8], the starting monothiomalondianilide **1** was synthesized by reacting commercially available acetoacetanilide with phenyl isothiocyanate (Scheme 1). The structure of compound **1** was confirmed by spectral data as well as X-ray diffraction analysis.



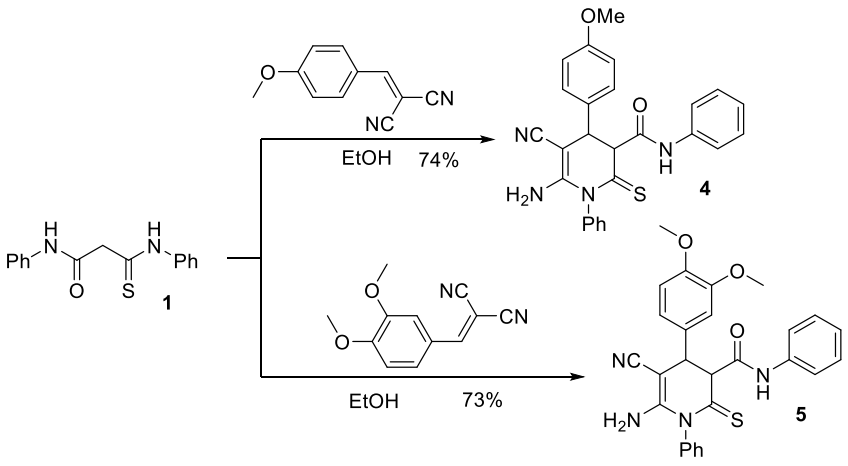
Scheme 1. XXX.

The reaction of thioamide **1** with arylidenemalononitriles **2**, either prepared via the Knoevenagel condensation (Method A), or in a multicomponent reaction involving aromatic aldehydes and malononitrile in the presence of a base (Method B), afforded cyclic Michael adducts, previously unreported nicotinamides **3** (Scheme 2).



Scheme 2. XXX.

We studied the capabilities of approaches **A** and **B** and found that they produce comparable yields. The highest yields of the target products were obtained for arylidene malononitriles with donor substituents. Thus, the reaction with (3,4-dimethoxybenzylidene)malononitrile and (4-methoxybenzylidene)malononitrile afforded products **4** and **5**, respectively (Scheme 3). In the future, it is planned to expand the library of products, as well as study their properties.



Scheme 3. XXX.

The structures of new compounds were also confirmed by spectral studies. For instance, Figures 1 and 2 show the ^{1}H and ^{13}C NMR spectra of compound **3** (Ar = 2-thienyl).

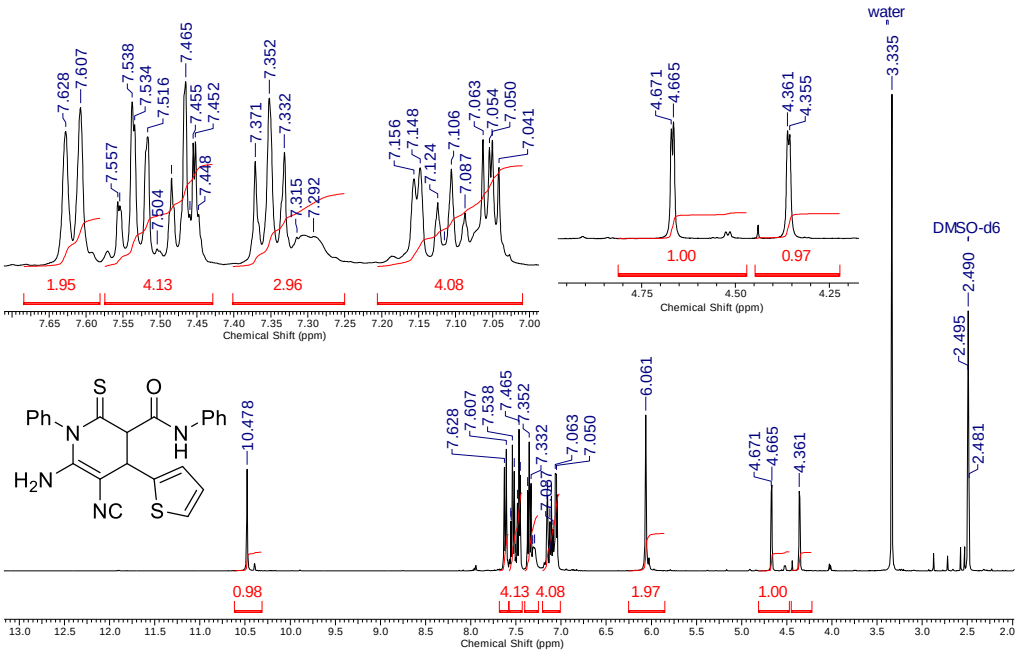


Figure 1. [1]H NMR spectrum of compound **3** (Ar = 2-thienyl).

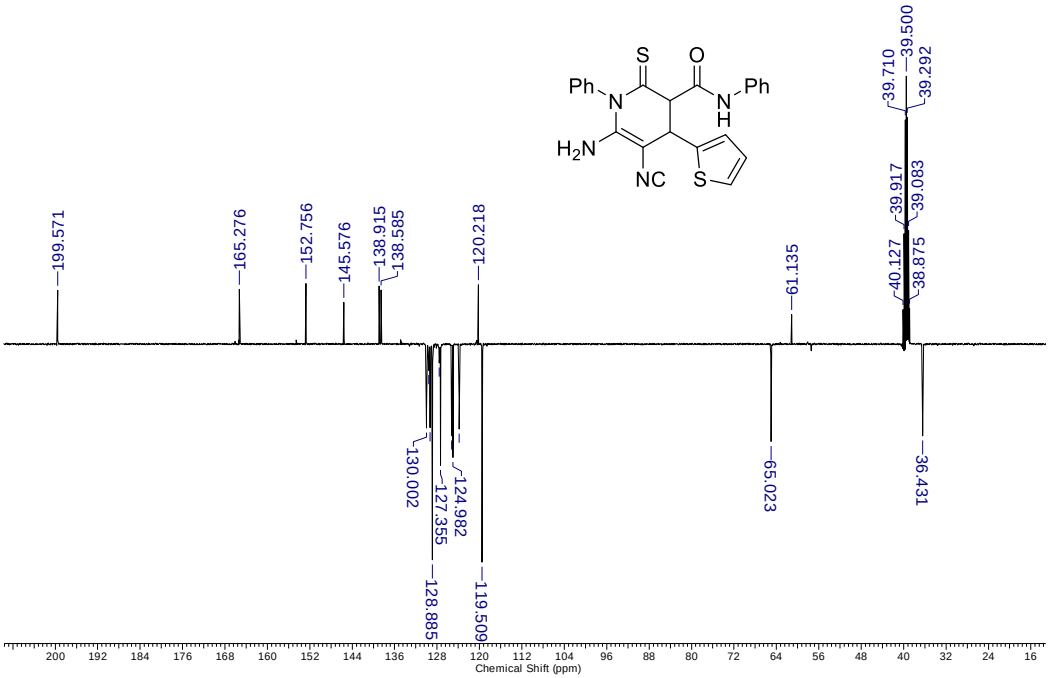


Figure 2. [13]C DEPTQ NMR spectrum of compound **3** (Ar = 2-thienyl).

We studied the capabilities of approaches **A** and **B** and found that they produce comparable yields. The highest yields of the target products were obtained for arylidene malononitriles with donor substituents. Thus, the reaction with (3,4-dimethoxybenzylidene)malononitrile and (4-methoxybenzylidene)malononitrile afforded products **4** and **5**, respectively (Scheme 3). In the future, it is planned to expand the library of products, as well as study their properties.

According to the results of molecular docking using the GalaxyWeb Sagittarius protocol, one of the products has affinity (ΔG = -22.586 kcal/mmol) to the protein complex H-Ras:SOS (PDB ID 6pf6, UniprotIDP04818), which indicates the potential prospects of studying the antitumor properties of the compound **3** (Ar = 4-MeOC$_6$H$_4$) (Figure 3).

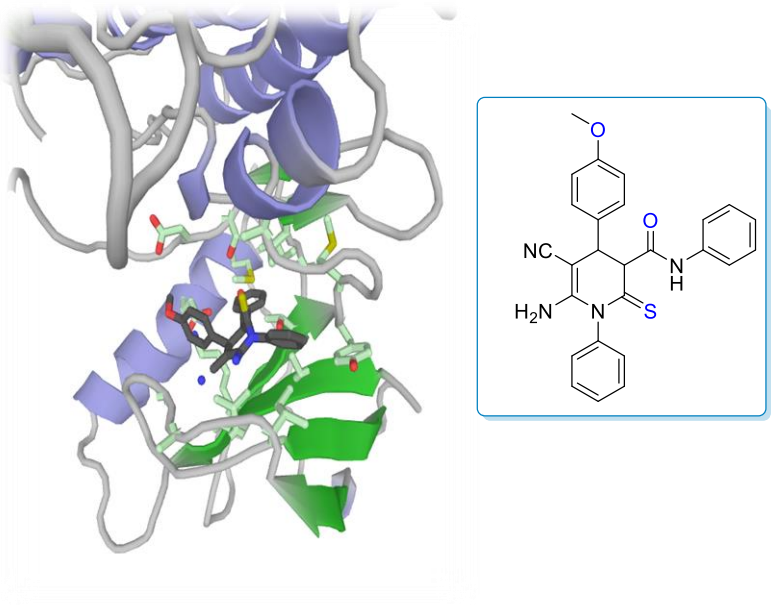
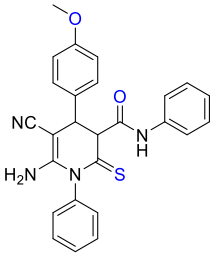


Figure 3. The predicted pose for the protein -ligand complex of H-Ras:SOS (PDB ID 6pf6, UniprotIDP04818) with compound **3** (Ar = 4-MeOC$_6$H$_4$).

3. Experimental

Synthesis of compounds 3 (Approach A). Arylidene malononitrile (0.03 mol) was dissolved in 12 mL of EtOH with gentle heating. Then monothiomalonanilide **1** (0.03 mol) was added followed by treatment with 0.03 mol of organic base (diethylamine, morpholine etc.) The mixture was stirred until starting reagent were consumed (TLC control), and left to stand overnight for crystallization. A yellow, fine crystalline powder was filtered off and washed with EtOH to give **3.** For analytical purposes, the product can be recrystallized from suitable solvent (acetone, MeCN, dioxane).

6-Amino-5-cyano-4-(4-methoxyphenyl)-N,1-diphenyl-2-thioxo-1,2,3,4-tetrahydropyridine-3-carboxamide (3) Ar = 4-MeOC$_6$H$_4$



NMR ^{1}H spectrum (400 MHz, DMSO-*d*$_6$), δ_H, ppm: 3.75 s (3H, MeO), 4.03 d (1H, CH Ar), 4.55 d (1H, C^{3}H), 5.94 br.s (2H, NH$_2$), 6.99-7.62 m (14H, 3 Ar), 10.40 br.s (1H, CONH).

NMR ^{13}C DEPTQ (DMSO-*d*$_6$), δ_C, ppm: 39.6* (CH); 55.1* (OCH$_3$); 60.6 (C^5); 64.9* (CH); 114.1* (2C, C^{3}H C^{5}H 4-MeOC$_6$H$_4$); 119.5* (2C, CH Ar); 120.5 (CN); 123.8* (CH Ph); 127.4* (CH Ph); 128.3* (2CH Ph); 128.8* (2CH Ph); 129.6* (2CH Ph); 130.0* (2CH Ph); 132.5 (C^1 Ar); 138.7 (C^1 Ar); 139.0 (C^1 Ar); 152.6 (C^6); 158.5 (C-OMe); 165.9 (CONH); 199.9 (C=S). *Signals in antiphase.

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editing, V.V.D.; visualization, V.V.D. and R.N.G.; supervision, V.V.D.; project administration, V.V.D. All authors have read and agreed to the published version of the manuscript.

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