

Synthesis of [1,3]Thiazolo[5,4-*b*]pyridine-2-carboxamides

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Abstract—[1,3]Thiazolo[5,4-*b*]pyridine-2-carboxamides were synthesized by reaction of 2-nitropyridin-3-amine with dithio esters containing a carbamoyl group.

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Fused systems containing a pyridine ring, in particular thiazolopyridines, are widely used as basis structures in the design of various biologically active compounds possessing antiviral, anticarcinogenic, anti-phlogistic, and antispasmodic properties [1–4], as well as of effective complexing agents and components of molecular systems sensitive to light and other physical factors [5]. Therefore, synthesis of new thiazolopyridine derivatives seems to be important.

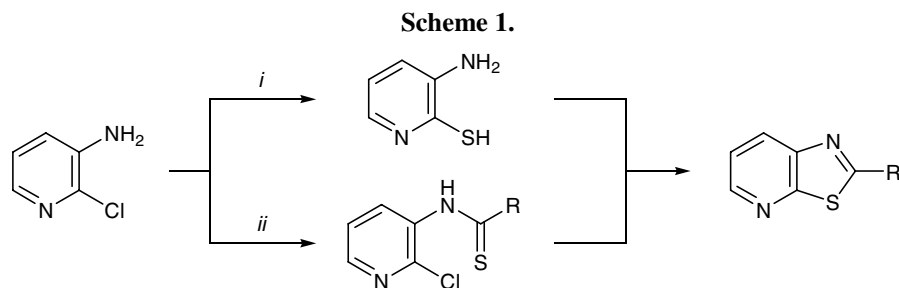
We recently reported on the formation of thiazolo[4,5-*b*]pyridine system via transformation of 1,2,4-triazine ring [6]. It was also shown that oxidation of compounds in which monothioamide fragment is linked to a heteroring leads to the formation of fused thiazole derivatives having a carboxamide group [7–9]. This approach was applied to the synthesis of previously unknown thiazolo[5,4-*b*]pyridines, and its sensitivity to electronic factors was noted [10, 11].

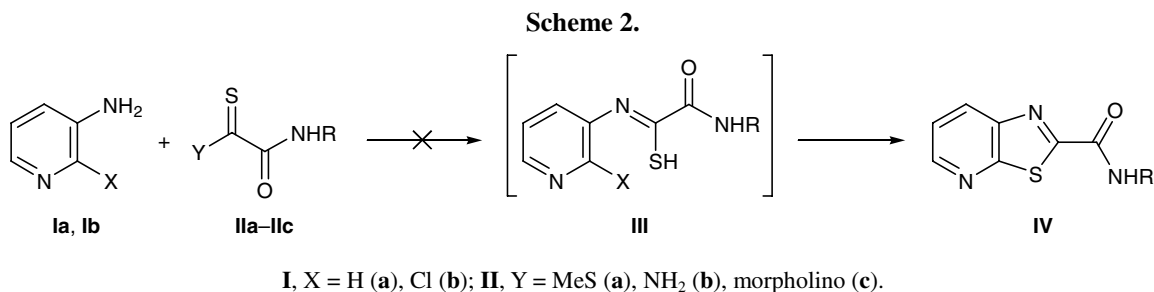
In the present work we made an attempt to synthesize [1,3]thiazolo[5,4-*b*]pyridine-2-carboxamides via nucleophilic aromatic substitution of both readily departing (as anion) groups and hydrogen atom [12]. It is known that thiazolopyridines can be obtained in two

steps, one of which is aromatic nucleophilic replacement of chlorine. In some procedures, the S_NAr reaction (replacement of the chlorine atom in aminochloropyridines) is the first step (Scheme 1, *i*) which is followed by thiazole ring closure by the action of carboxylic acid chlorides [13]. According to other methods, intramolecular nucleophilic replacement of halogen is the second step (Scheme 1, *ii*), e.g., in the reaction of 3-amino-2-chloropyridines with *O*-alkyl carbothioates; in this case, preliminary activation of the amino group by the action of butyllithium or sodium hydride is required [14].

We presumed that tandem reactions of 3-amino-pyridines with difunctional reagents possessing both electrophilic and nucleophilic centers could provide a convenient one-pot procedure for the synthesis of thiazolopyridines. As such reagents we selected monothioamides and dithioamates. No analogous reactions leading to thiazolecarboxamides have been reported so far.

We examined reactions of dithioester **IIa** and monothioamides **IIb** and **IIc** with 3-aminopyridine (**Ia**) and 3-amino-2-chloropyridine (**Ib**) (Scheme 2).



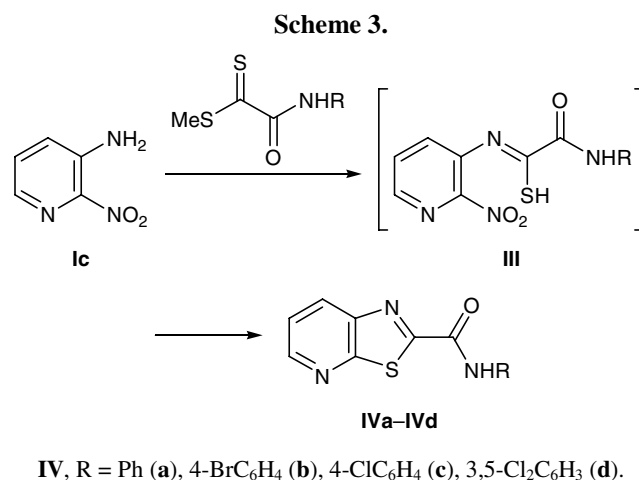


We expected that the first reaction step would be thioacylation of the amino group in pyridines **I** with formation of compounds **III** and that the second step would be heterocyclization to give the desired thiazolopyridine system **IV**. Reactions of monothiooxamides and dithiooxamates with 3-aminopyridine (**Ia**) having no substituent on C² were carried out in the presence of oxidants [K₃Fe(CN)₆ or MnO₂] under the conditions developed previously for S_N^H reactions with π -deficient aromatic systems [12, 15, 16]. However, we failed to isolate the desired thiazolopyridines: either the initial compounds or complex mixtures of unidentified products were obtained.

Reactions of 3-aminopyridines **Ia** and **Ib** with monothiooxamides and dithiooxamates, as well as of 3-amino-2-nitropyridine (**Ic**) with monothiooxamides, were performed in the following solvents: mesitylene, dioxane, THF, benzene, pyridine, collidine, butan-1-ol, *tert*-butyl alcohol, or their mixtures with xylene; triethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), NaH, Na₂CO₃, and Cs₂CO₃ were tried as bases. However, in all cases only the initial aminopyridine was recovered from the reaction mixture.

Experiments with 3-amino-2-nitropyridine (**Ic**) and dithiooxamates (Scheme 3) were more successful. By heating a solution of **Ic** and *S*-methyl *N*-aryldithiooxamates in xylene in the presence of Cs₂CO₃ for 3 h we obtained thiazolopyridines **IVa–IVd** in 64–76% yield (calculated on the reacted aminopyridine **Ic**, the conversion being 50%). The substituent on the nitrogen atom in the carbamoyl fragment did not exert an appreciable effect on the product yield. On the other hand, the yield of thiazolopyridines strongly depended on the reaction conditions. Access of atmospheric oxygen is crucial: no thiazolopyridines were formed when the reactions were carried out under argon. Thiazolopyridines were not formed in other solvents or in the presence of other bases; in the best case, their yield was very poor. These findings suggest fairly complex mechanism of the process which is likely to involve radical ion species. Taking into account that

neither 3-aminopyridine nor 3-amino-2-chloropyridine and 3-amino-5-nitropyridine reacted with dithioesters (only the initial compounds were isolated from the reaction mixture), we presume that the determining stage of the process is thioacylation of the amino group.



EXPERIMENTAL

The ¹H NMR spectra were recorded on Bruker WM-200 (200 MHz) and WM-250 (250 MHz) spectrometers from solutions in DMSO-*d*₆; the ¹³C NMR spectra were measured on a Bruker AC-200 instrument (50 MHz) using the same solvent. The mass spectra (electron impact, 70 eV) were obtained on a Varian MAT CH-6 mass spectrometer with direct sample admission into the ion source (control voltage 1.75 kV). The melting points were determined on a Boetius melting point apparatus; uncorrected values are given. The reaction mixtures and products were analyzed by thin-layer chromatography on Silufol UV-254 plates using ethyl acetate–petroleum ether (1:3) as eluent.

General procedure for the synthesis of thiazolopyridines IVa–IVd. The corresponding *S*-methyl *N*-aryldithiooxamate, 0.3 mmol, and cesium carbonate, 0.1 mmol, were added at 20–25°C to a solution of 0.1 mmol of 2-nitropyridin-3-amine (**Ic**) in 2 ml of

xylylene. The mixture was stirred for 3 h at 140°C and evaporated, and the residue was purified by preparative thin-layer chromatography on silica gel using ethyl acetate–petroleum ether (2:1) as eluent.

***N*-Phenyl[1,3]thiazolo[5,4-*b*]pyridine-2-carboxamide (IVa).** Yield 67%, mp 146°C, R_f 0.34. ^1H NMR spectrum, δ , ppm: 7.2 t (1H, H_{arom}), 7.4 t (2H, H_{arom}), 7.75 q (1H, Py), 7.95 d (2H, H_{arom}), 8.6 d (1H, Py), 8.8 d (1H, Py), 11.25 s (1H, NH). ^{13}C NMR spectrum, δ_{C} , ppm: 120.9 (C^{14} , C^{18}), 122.8 (C^8), 124.7 (C^{16}), 128.8 (C^{15} , C^{17}), 132.1 (C^9), 137.7 (C^{13}), 145.9 (C^7), 149.5 (C^4), 157.8 (C^{10} , C^5), 164.8 (C^2). Mass spectrum: m/z 255 [M] $^+$. Found, %: C 61.10; H 3.45; N 16.35; S 12.37. $\text{C}_{13}\text{H}_9\text{N}_3\text{OS}$. Calculated, %: C 61.16; H 3.55; N 16.46; S 12.56. M 255.29.

***N*-(4-Bromophenyl)[1,3]thiazolo[5,4-*b*]pyridine-2-carboxamide (IVb).** Yield 76%, mp 151°C, R_f 0.36. ^1H NMR spectrum, δ , ppm: 7.55 m (2H, H_{arom}), 7.65 m (2H, Py), 7.8 m (1H, H_{arom}), 8.60 d (1H, Py), 8.8 d (1H, Py), 11.35 s (1H, NH). ^{13}C NMR spectrum, δ_{C} , ppm: 122.1 (C^{16}), 122.4 (C^8), 122.7 (C^{14} , C^{18}), 125.2 (C^{15} , C^{17}), 131.5 (C^9), 132.0 (C^7), 137.0 (C^4), 145.8 (C^{10}), 157.8 (C^2). Mass spectrum: m/z 335 [M] $^+$. Found, %: C 46.60; H 2.28; N 12.42; S 9.37. $\text{C}_{13}\text{H}_8\text{BrN}_3\text{OS}$. Calculated, %: C 46.72; H 2.41; N 12.57; S 9.59. M 334.19.

***N*-(4-Chlorophenyl)[1,3]thiazolo[5,4-*b*]pyridine-2-carboxamide (IVc).** Yield 64%, mp 178°C, R_f 0.32. ^1H NMR spectrum, δ , ppm: 7.45 d (2H, H_{arom}), 7.75 t (1H, Py), 7.95 d (2H, H_{arom}), 8.6 d (1H, Py), 8.8 d (1H, Py), 11.25 s (1H, NH). ^{13}C NMR spectrum, δ_{C} , ppm: 122.4 (C^{14} , C^{18}), 128.4 (C^{16}), 128.7 (C^{15} , C^{17}), 132.1 (C^9), 136.7 (C^{13}), 145.8 (C^7), 149.5 (C^4), 157.9 (C^5 , C^{10}), 164.4 (C^2). Mass spectrum: m/z 289 [M] $^+$. Found, %: C 53.70; H 2.78; N 14.33; S 10.89. $\text{C}_{13}\text{H}_8\text{ClN}_3\text{OS}$. Calculated, %: C 53.89; H 2.78; N 14.50; S 11.07. M 289.74.

***N*-(3,5-Dichlorophenyl)[1,3]thiazolo[5,4-*b*]pyridine-2-carboxamide (IVd).** Yield 68%, mp 193°C, R_f 0.47. ^1H NMR spectrum, δ , ppm: 7.4 s (1H, H_{arom}), 7.75 q (2H, Py), 8.05 s (2H, H_{arom}), 8.6 d (1H, Py), 8.85 d (1H, Py), 11.45 s (1H, NH). ^{13}C NMR spectrum, δ_{C} , ppm: 111.6 (C^8), 114.0 (C^{14} , C^{18}), 118.9 (C^{13}), 122.7 (C^9), 123.8 (C^{16}), 132.0 (C^7), 133.9 (C^4), 134.0 (C^{10}), 149.5 (C^5), 158.1 (C^2). Mass spectrum: m/z 324 [M] $^+$. Found, %: C 48.00; H 1.95; N 12.80; S 9.66. $\text{C}_{13}\text{H}_7\text{Cl}_2\text{N}_3\text{OS}$. Calculated, %: C 48.16; H 2.18; N 12.96; S 9.89. M 324.18.

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