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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, antiphlogistic, 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.

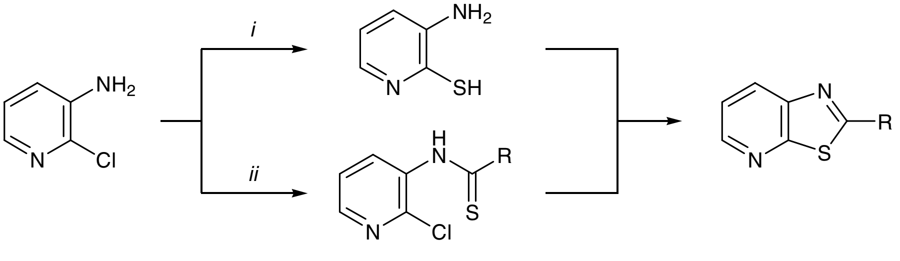
We recently reported on the formation of thiazolo[4,5-*b*]pyridine system via transformation of 1,2,4-triazine ring [6]. It was also shown that oxidation of compounds in which monothiooxamide fragment is linked to a heteroring leads to the formation of fused thiazole derivatives having a carboxamide 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].

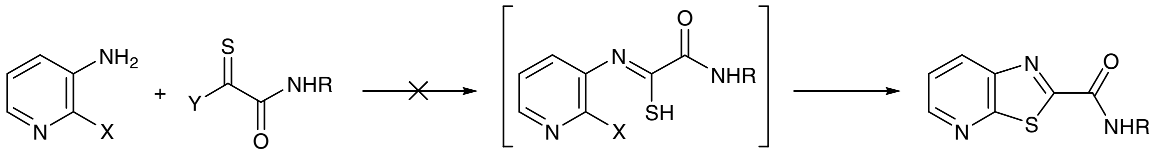
We presumed that tandem reactions of 3-aminopyridines with difunctional reagents possessing both electrophilic and nucleophilic centers could provide a convenient one-pot procedure for the synthesis of thiazolopyridines. As such reagents we selected monothiooxamides and dithiooxamates. No analogous reactions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

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

Scheme 1.



Scheme 2.



Ia, **Ib** **IIa–IIc** **III** **IV**

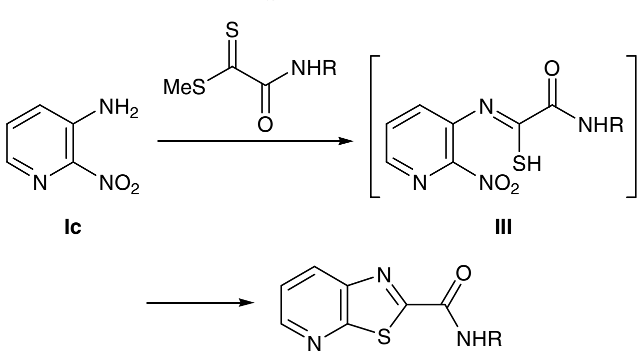
I, X = H (**a**), Cl (**b**); **II**, Y = MeS (**a**), NH_2 (**b**), morpholino (**c**).

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 C^2 were carried out in the presence of oxidants [$K_3Fe(CN)_6$ or MnO_2] 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, Na_2CO_3, and Cs_2CO_3 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 Cs_2CO_3 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.

Scheme 3.



Ic **III** **IVa–IVd**

IV, R = Ph (**a**), 4-BrC_6H_4 (**b**), 4-ClC_6H_4 (**c**), 3,5-$Cl_2C_6H_3$ (**d**).

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 ^{13}C 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 xylene. 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. ^{1}H 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. $C_{13}H_9N_3OS$. 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. ^{1}H 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. $C_{13}H_8BrN_3OS$. 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. ^{1}H 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. $C_{13}H_8ClN_3OS$. 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. ^{1}H 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. $C_{13}H_7Cl_2N_3OS$. Calculated, %: C 48.16; H 2.18; N 12.96; S 9.89. *M* 324.18.

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REFERENCES

1. Mylari, B.L., Larson, E.R., Beyer, T.A., Zembrowski, W.J., Aldinger, C.E., Dee, M.F., Siegel, T.W., and Singleton, D.H., *J. Med. Chem.*, 1991, vol. 34, p. 108.
2. Borthwick, A.D., Davies, D.E., Ertl, P.F., Exall, A.M., Haley, T.M., Hart, G.J., Jackson, D.L., Parry, N.R., Patikis, A., Trivedi, N., Weingarten, G.G., and Woolven, J.M., *J. Med. Chem.*, 2003, vol. 46, p. 4428.
3. Ternansky, R.J., Draheim, S.E., Pike, A.J., et al., *J. Med. Chem.*, 1993, vol. 36, p. 1971.
4. Alvarez-Ibarra, C., Fernández-Granda, R., Quiroga, M.L., Carbonell, A., Cárdenas, F., and Giralt, E., *J. Med. Chem.*, 1997, vol. 40, p. 668.
5. *Comprehensive Heterocyclic Chemistry II*, Katritzky, A.R., Rees, C.W., and Scriven, E.F.V., Eds., Oxford: Pergamon, 1996, vol. 5, p. 4.
6. Krayushkin, M.M., Yarovenko, V.N., Sedishev, I.P., Andreiko, A.A., Mochulskaya, N.N., and Charushin, V.N., *Mendeleev Commun.*, 2005, no. 4, p. 151.
7. Smirnova, N.G., Zavarzin, I.V., and Krayushkin, M.M., *Khim. Geterotsikl. Soedin.*, 2006, p. 167.
8. Yarovenko, V.N., Smirnova, N.G., Bulgakova, V.N., Zavarzin, I.V., and Krayushkin, M.M., *Russ. J. Org. Chem.*, 2003, vol. 39, p. 1161.
9. Smirnova, N.G., Zavarzin, I.V., Yarovenko, V.N., and Krayushkin, M.M., Abstracts of Papers, *I Molodezhnaya konferentsiya Instututa organicheskoi khimii Rossiiskoi Akademii Nauk* (Ist Youth Conf. of the Institute of Organic Chemistry, Russian Academy of Sciences), Moscow, 2005, p. 118.
10. Zavarzin, I.V., Smirnova, N.G., Yarovenko, V.N., and Krayushkin, M.M., *Izv. Ross. Akad. Nauk, Ser. Khim.*, 2004, p. 1299.
11. Zavarzin, I.V., Smirnova, N.G., Yarovenko, V.N., and Krayushkin, M.M., *Russ. J. Org. Chem.*, 2006, vol. 42, p. 273.
12. Chupakhin, O.N., Charushin, V.N., and van der Plas, H.C., *Nucleophilic Aromatic Substitution of Hydrogen*, San Diego: Academic, 1994.
13. Suzuki, N. and Dohmori, R., *Chem. Pharm. Bull.*, 1979, vol. 27, p. 410.
14. Kulkarni, D.G., Lokhande, S.R., and Khadse, B.G., *Indian J. Pharm.*, 1981, vol. 43, p. 37.
15. Charushin, V.N., Alexeev, A.G., Chupakhin, O.N., and van der Plas, H.C., *Adv. Heterocycl. Chem.*, 1989, vol. 46, p. 73.
16. Chupakhin, O.N., Charushin, V.N., and Rusinov, V.L., *Sovremennyi organicheskii sintez* (Contemporary Organic Synthesis), Moscow: Khimiya, 2003, p. 99.