ISSN 1070-4280 Russian Journal of Organic Chemistry, 2006, Vol. 42, No. 2, pp. 273–274. © Pleiades Publishing, Inc. 2006.
Original Russian Text © I.V. Zavarzin, N.G. Smirnova, V.N. Yarovenko, M.M. Krayushkin, 2006, published in Zhurnal Organicheskoi Khimii, 2006, Vol. 42, no. 2, pp. 288–289.

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

I.V. Zavarzin, N.G. Smirnova, V.N. Yarovenko, and M.M. Krayushkin

Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Moscow, 119991 Russia
e-mail: zavi@mail.ioc.ac.ru

Received March 23, 2005

Abstract—A convenient procedure was developed for preparation of thiazolo[5,4-*b*]pyridine-2-carboxamides by oxidation of monothiooxamides synthesized from 3-aminopyridine.

DOI: 10.1134/S1070428002120205

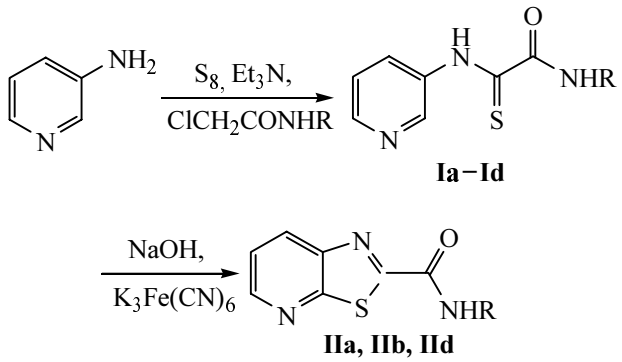
We formerly demonstrated that the oxidation of compounds where monothiooxamide fragments are linked to phenyl or heterocyclic rings afforded in good yields fused compounds with a carboxamide function. Just in this fashion were prepared carbamoylbenzothiazoles [1], and based on isomeric aminothiophenes carbamoyl derivatives of thieno[3,2-*d*]- and -[2,3-*d*]thiazoles were synthesized [2, 3]. We extended this approach also to aminopyridines: the previously unknown 5-aminothiazolo[4,5-*b*]pyridine-2-carboxamides were obtained from 2,6-diaminopyridine [4].

In this study we applied this method to the preparation of thiazolo[5,4-*b*]pyridine-2-carboxamides from monothiooxamides obtained from 3-aminopyridine. The derivatives of thiazolopyridines are known to exhibit a wide range of biological activity including analgesic, antipyretic, antiphlogistic, and antifungal action [5, 6]. At the same time the published procedure for the synthesis of pyrido-[3,2-*d*]thiazole-2-carboxamide is very laborious and multistage [7]. The approach we developed provides the compounds of this structure in much better yield and only in two stages.

The initial monothiooxamides **Ia–Id** were prepared by the reaction of 3-aminopyridine with chloroacetamides and sulfur in the presence of triethylamine along the procedure we had developed before [1–4].

The oxidation of monothiooxamides **Ia, Ib**, and **Id** giving a thiazole system is effected by $K_3Fe(CN)_6$ in 20% solution of NaOH at 20°C and furnished in good yields thiazolo[5,4-*b*]-pyridine-2-carboxamides **IIa, IIb**, and **IId**.

The structure of compounds **Ia–Id** and **IIa, IIb**, and **IId** is confirmed by elemental analysis, ^{1}H NMR and mass spectra. In the mass spectra of compounds **Ia–Id** and **IIa, IIb**, and **IId** the molecular ion peaks are present.



R = Ph (**a**), 4-FC_6H_4 (**b**), 2,6-$(Me)_2C_6H_3$(**c**), 4-BrC_6H_4 (**d**).

EXPERIMENTAL

^{1}H NMR spectra were registered on a spectrometer Bruker AC-300 (operating frequency 300 MHz) from solutions in $CDCl_3$ and DMSO-d_6. Mass spectra were recorded on Kratos instrument with a direct admission of a sample into the ion source, ionizing electrons energy 70 eV, control voltage 1.75 kV. The reagents used in the study are commercial products purchased from Acros.

Monothiooxamides Ia–Id. To a preliminary prepared mixture of 0.5 g (5.3 mmol) of 3-aminopyridine, 1.0 g of sulfur, and 1 ml of Et_3N in 5 ml of DMF was added 4.4 mmol of an appropriate chloroacetamide, the mixture was stirred for 8 h at 20°C and then diluted with water. The separated precipitate was filtered off, washed with water, dried, dissolved in 10 ml of acetone, and filtered. The acetone was removed, the residue was recrystallized from 95% EtOH. Yields are reported with respect to the initial chloroacetamide.

***N*-Phenyl-2-(pyridin-3-ylamino)-2-thioxoacetamide (Ia).** Yield 60%, mp 169–171°C (EtOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.20 m ($1H_{arom}$), 7.40 m ($2H_{arom}$), 7.55 m ($1H_{pyridine}$), 7.85 d ($2H_{arom}$, *J* 7.78 Hz),

8.38 d (1$H_{pyridine}$, *J* 7.86 Hz), 8.55 d (1$H_{pyridine}$, *J* 3.93 Hz), 9.00 s (1$H_{pyridine}$), 10.50 s (1H, NH), 12.52 s (1H, NH). Mass spectrum, *m*/*z*: 257 $[M]^+$. Found, %: C 60.46; H 4.50; N 16.54; S 12.22. $C_{13}H_{11}N_3OS$. Calculated, %: C 60.68; H 4.31; N 16.33; S 12.46.

***N*-(4-Fluorophenyl)-2-(pyridin-3-ylamino)-2-thioxoacetamide (Ib).** Yield 65%, mp 184–186°C (EtOH). ^{1}H (DMSO-d_6), δ, ppm: 7.25 m (2H_{arom}), 7.52 m (1$H_{pyridine}$), 7.83 m (2H_{arom}), 8.35 d (1$H_{pyridine}$, *J* 8.04 Hz), 8.50 d (1$H_{pyridine}$, *J* 4.53 Hz), 9.00 s (1$H_{pyridine}$), 10.65 s (1H, NH), 12.60 s (1H, NH). Mass spectrum, *m*/*z*: 275 $[M]^+$. Found, %: C 56.66; H 3.40; N 15.44. $C_{13}H_{10}FN_3OS$. Calculated, %: C 56.72; H 3.66; N 15.26.

***N*-(2,6-Dimethylphenyl)-2-(pyridin-3-ylamino)-2-thioxoacetamide (Ic).** Yield 70%, mp 143–145°C (EtOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.22 s (6H, 2 CH_3), 7.15 m (3H_{arom}), 7.50 m (1$H_{pyridine}$), 8.40 d (1$H_{pyridine}$, *J* 8.26 Hz), 8.50 d (1$H_{pyridine}$, *J* 4.70 Hz), 9.02 d (1$H_{pyridine}$, *J* 2.31 Hz), 10.11 s (1H, NH), 12.42 s (1H, NH). Mass spectrum, *m*/*z*: 285 $[M]^+$. Found, %: C 63.46; H 5.50; N 14.54; S 11.07. $C_{15}H_{15}N_3OS$. Calculated, %: C 63.13; H 5.30; N 14.73; S 11.24.

***N*-(4-Bromophenyl)-2-(pyridin-3-ylamino)-2-thioxoacetamide (Id).** Yield 65%, mp 170–172°C (EtOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.50 m (1$H_{pyridine}$), 7.60 d (2H_{arom}, *J* 8.77 Hz), 7.80 d (2H_{arom}, *J* 8.78 Hz), 8.35 d (1$H_{pyridine}$, *J* 8.32 Hz), 8.50 d (1$H_{pyridine}$, *J* 4.87 Hz), 9.00 d (1$H_{pyridine}$, *J* 2.34 Hz), 10.70 s (1H, NH), 12.60 s (1H, NH). Mass spectrum, *m*/*z*: 336 $[M]^+$. Found, %: C 46.78; H 3.20; Br 23.90; N 12.34; S 9.32. $C_{13}H_{10}BrN_3OS$. Calculated, %: C 46.44; H 3.00; Br 23.77; N 12.50; S 9.54.

Thiazolo[5,4-*b*]pyridin-2-carboxamides IIa, IIb, and **IId.** A solution of 1.0 mmol of monothiooxamide **Ia, Ib**, and **Id** in 20% water solution of NaOH (8.4 mmol) was added dropwise at 20°C while stirring to a solution of 0.72 g (2.2 mmol) of $Q_3Fe(CN)_6$ in 5 ml of water, and the resulting reaction mixture was stirred for 8 h more. The precipitated thiazolopyridines **IIa, IIb**, and **IId** were filtered off,washed with water, dried, and recrystallized from 95% EtOH.

***N*-Phenyl[1,3]thiazolo[5,4-*b*]pyridin-2-carboxamide (IIa).** Yield 51%, mp 124–126°C (EtOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.20 m (1H_{arom}), 7.42 m (2H_{arom}), 7.76 m (1$H_{pyridine}$), 7.93 d (2H_{arom}, *J* 7.82 Hz), 8.65 d (1$H_{pyridine}$, *J* 7.79 Hz), 8.83 s (1$H_{pyridine}$), 11.20 s, (1H, NH). Mass spectrum, *m*/*z*: 255 $[M]^+$. Found, %: C 61.36, H 3.30; N 16.74; S 12.82. $C_{13}H_9N_3OS$. Calculated, %: C 61.16; H 3.55; N 16.46; S 12.56.

***N*-(4-Fluorophenyl)[1,3]thiazolo[5,4-*b*]pyridin-2-carboxamide (IIb).** Yield 50%, mp 188–190°C (EtOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.59 d (2H_{arom}, *J* 8.65 Hz), 7.75 m (1$H_{pyridine}$), 7.95 d (2H_{arom}, *J* 8.74 Hz), 8.63 d (1$H_{pyridine}$, *J* 8.30 Hz), 8.84 d (1$H_{pyridine}$, *J* 4.19 Hz), 11.39 s, (1H, NH). Mass spectrum, *m*/*z*: 273 $[M]^+$. Found, %: C 57.50; H 2.70; N 15.14. $C_{13}H_8FN_3OS$. Calculated, %: C 57.13; H 2.95; N 15.38.

***N*-(4-Bromophenyl)[1,3]thiazolo[5,4-*b*]pyridin-2-carboxamide (IId).** Yield 55%, mp 179–180°C (EtOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.59 d (2H_{arom}, *J* 8.68 Hz), 7.76 m (1$H_{pyridine}$), 7.92 d (2H_{arom}, *J* 8.72 Hz), 8.62 d (1$H_{pyridine}$, *J* 8.54 Hz), 8.81 d (1$H_{pyridine}$, *J* 3.46 Hz), 11.28 s, (1H, NH). Mass spectrum, *m*/*z*: 334 $[M]^+$. Found, %: C 46.86; H 2.30; Br 23,66; N 12.74; S 9.42. $C_{13}H_8BrN_3OS$. Calculated, %: C 46.72; H 2.41; Br 23.91; N 12.57; S 9.60.

The study was carried out under financial support of ISTC (grant no. 2117).

REFERENCES

1. Yarovenko, V.N., Stoyanovich, F.M., Zolotarskaya, O.Yu., Chernoburova, E.I., Zavarzin, I.V., and Krayushkin, M.M., *Izv. Akad. Nauk, Ser. Khim.,* 2002, p. 136.
2. Yarovenko, V.N., Smirnova, N.G., Bulgakova, V.N., Zavarzin, I.V., and Krayushkin, M.M., *Zh. Org. Khim.,* 2003, vol. 39, p. 1232.
3. Zavarzin, I.V., Smirnova, N.G., Yarovenko, V.N., and Krayushkin, M.M. *Zh. Org. Khim.,* 2004, vol. 40, p. 146.
4. Zavarzin, I.V., Smirnova, N.G., Yarovenko, V.N., and Krayushkin, M.M., *Izv. Akad. Nauk, Ser. Khim.,* 2004, p. 1299.
5. El-Hiti, Gamal, A., *Monatsh. Chem.,* 2003, vol. 134, p. 837.
6. Ulrich. H., *Sci. Synthes.,* 2002, vol. 11, p. 835.
7. Fridman, C.G., *Zh. Obshch. Khim.,* 1956, vol. 26, p. 864.