Oxidative Cyclization of *N*-Methyl- and *N*-Benzoylpyridylthioureas. Preparation of New Thiazolo[4,5-*b*] and [5,4-*b*]pyridine Derivatives.

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Cyclization of *N*-methyl- and *N*-benzoylpyridylthioureas, prepared from the corresponding aminopyridines, has been realized using various conditions. With bromine in acetic acid or potassium ferricyanide, the cyclization occurred on the nitrogen of the pyridine ring and pyridinium salts or 1,2,4-thiadiazolo[2,3-*a*]pyridylidene systems were obtained. On the other hand, treatment of the thioureas with sodium methoxide in *N*-methylpyrrolidinone (NMP) led to formation of thiazolo[4,5-*b*] and [5,4-*b*]pyridines, which are interesting targets for biological evaluation.

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Introduction.

Synthetic and naturally occurring heterocyclic compounds often possess various biological activities, and more particularly those containing thiazole or benzothiazole rings. For instance, compounds such as **1** have been found to be antitumoral [1] whereas **2** is known for its anticonvulsant action [2]. On the other hand, heterocyclic amines also present some biological properties [3] and specifically the bicyclic amine 2-amino-1-methyl-6-phenylimidazolo[4,5-*b*]pyridine (PhIP) (**3**) has mutagenic activity [4]. Therefore it is of interest to prepare thiazole-containing analogues of PhIP and to study their biological properties. In view of these considerations, syntheses of molecules such as **4** and **5** were scheduled (Figure 1).

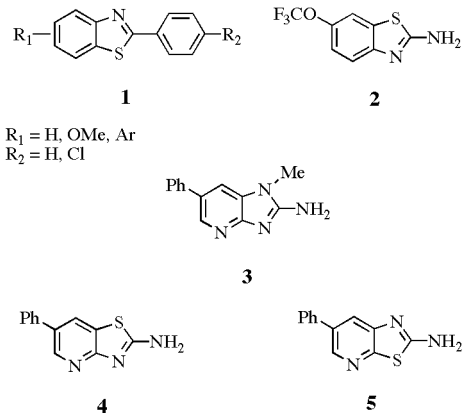
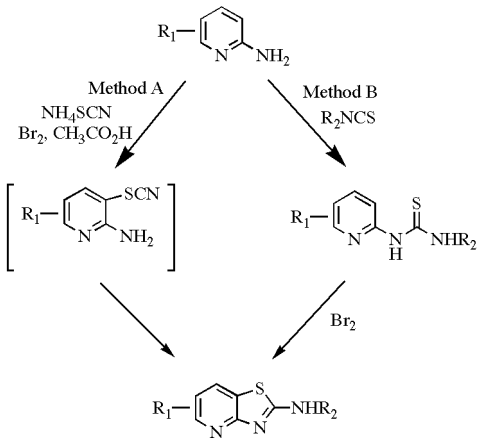


Figure 1

Literature studies revealed that two principal routes have been used for the synthesis of such bicyclic systems. Thus, various thiazolo[4,5-*b*]pyridines can be formed by a one-step procedure starting from the appropriate aminopyridines. Reacting them with a thiocyanate salt in acetic acid with bromine led to the formation of the corresponding thiocyanated intermediates, which then spontaneously cyclized under the reaction conditions [5-8] (Scheme 1, Method A). The success of the reaction has been reported to depend upon the activation of the pyridine ring [7]. On the other hand, a two-step procedure was also described: a thiourea derivative was obtained from the reaction between an aminopyridine and an appropriate isothiocyanate which was subsequently cyclized by bromine in acetic acid or chloroform [9] (Scheme 1, Method B). If a halogen atom is present at the α position to the amino group, the cyclization occurs spontaneously [10,11].

Scheme 1



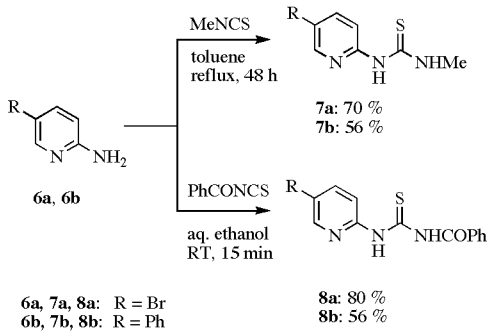
This last method was chosen in order to get the required heterocyclic amines **4** and **5**.

Results and Discussion.

In order to study the influence of the substrate on the cyclization step, various 5-substituted pyridylthioureas were prepared. Thus, 2-amino-5-phenylpyridine (**6b**) was first obtained by Suzuki cross-coupling of 2-amino-5-bromopyridine (**6a**) with benzeneboronic acid [12]. Both of these aminopyridines, **6a** and **6b**, were then used to get the corresponding pyridylthioureas (Scheme 2). Treatment of **6a** and **6b** with methyl isothiocyanate in toluene led to the formation of the *N*-methylpyridylthioureas **7a** and **7b** with yields of 70 % and 56 %, respectively. In the same way, the

N-benzoylpyridylthioureas **8a** and **8b** were obtained by reaction of **6a** and **6b** with benzoyl isothiocyanate in aqueous ethanol, with yields of 80 % and 56 %.

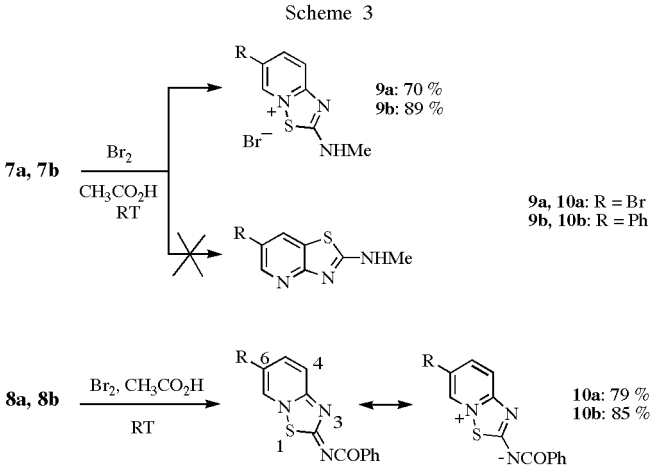
Scheme 2



With these *N*-methyl- and *N*-benzoylpyridylthioureas in hand, we then continued the sequence with the cyclization step. The first method chosen for this purpose was the Hugershoff reaction, which has been widely used to obtain benzothiazoles [13]. Thus, when compound **7a** was reacted with bromine in acetic acid at room temperature a beige solid was obtained with 70 % yield after

work-up. Examination of the NMR data led to the conclusion that a cyclization had occurred but on the nitrogen atom of the pyridine ring and thus the pyridinium salt **9a** was formed rather than the expected thiazolopyridine. Indeed, in compound **9a**, the H-6 proton of the pyridine ring is strongly deshielded from 8.30 ppm to 9.42 ppm. Similar results were obtained with the *N*-methylpyridylthiourea **7b** on one hand and the *N*-benzoylpyridylthioureas **8a** and **8b** on the other hand. For these latter compounds, the absence of a labile proton in the ^{1}H NMR spectra led us to assume the thiadiazolopyridylidene structures shown in Scheme 3 for **10a** and **10b**.

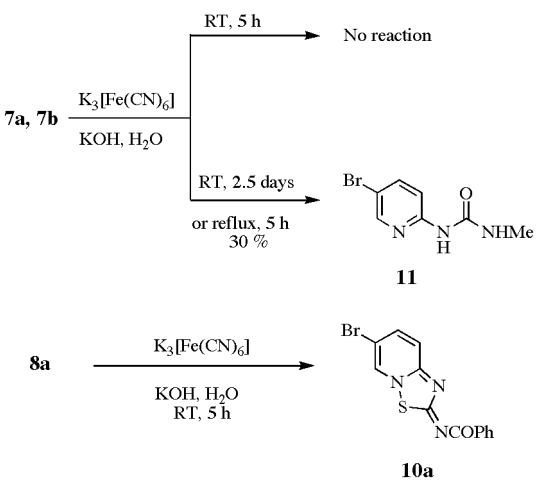
Scheme 3



Despite the results reported by Sarkis and Faisal [9], where the same method was used to prepare various thiazolopyridines, the formation of the pyridinium salts under the conditions used here was not surprising. A survey of the literature showed that similar pyridinium salts have been prepared by oxidative cyclization of unsubstituted pyridylthioureas with bromine in acetic acid, chloroform or methanol or with sulfuryl chloride in toluene [14,15].

Nevertheless, we decided to use another well-known reaction for such a cyclization, the Jacobson reaction, with potassium ferricyanide as oxidative agent [16]. When the pyridylthiourea **7a** was stirred at room temperature under the Jacobson conditions, the starting material was recovered unchanged after 5 hours. If the reaction medium was submitted to prolonged stirring or refluxing, compound **11** was isolated with 30 % yield in both cases, with some recovered starting material. The formation of **11** corresponds to the hydrolysis of the thiocarbonyl group of **7a** by the hydroxide used during the reaction (Scheme 4).

Scheme 4

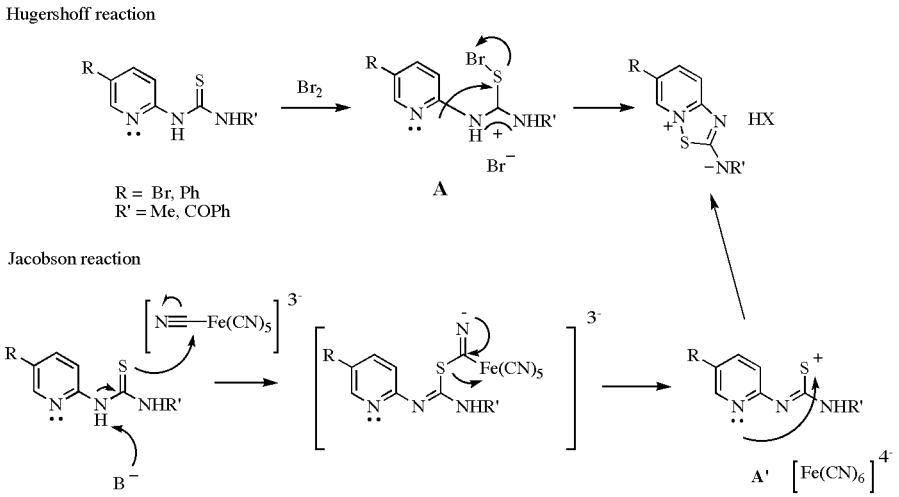


In the same way, no reaction was observed when **7b** was stirred at room temperature with potassium ferricyanide during 5 hours. On the contrary, when the *N*-benzoylpyridylthiourea **8a** was reacted under the same conditions, the cyclization occurred once again on the nitrogen of the pyridine ring, and the corresponding product **10a** was obtained quantitatively (Scheme 4).

It consequently appeared that the targeted thiazolopyridine structures could not be prepared by either Hugershoff or Jacobson reactions, whatever the subtitution of the pyridine ring or of the thiourea was. An explanation for the

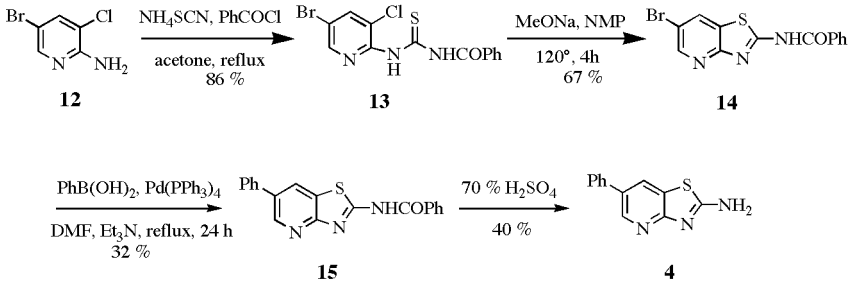
favoured formation of pyridinium salts can be furnished by consideration of the reaction mechanisms [17] (Scheme 5).

Scheme 5



In the Hugershoff reaction, the oxidation of the initial thiourea with bromine led to the formation of structure **A**, in which the sulfur atom is electrophilic. In the same way, in the Jacobson conditions, thioenolization and attack of the ferricyanide anion resulted in the transient species **A'** with an electrophilic sulfur. The subsequent cyclization is then performed on the more nucleophilic nitrogen atom of the pyridine ring rather than the C-3 carbon. It would be better therefore to get an intermediate with a nucleophilic sulfur that can then react on the pyridine ring. This was realised when the reaction was carried out under basic conditions, by abstraction of one of the labile hydrogen of the thiourea and formation of a thiolate anion. Nevertheless, treatment of **8a** with sodium methoxide in *N*-methylpyrrolidinone (NMP) at 120° during 4 hours did not give the expected thiazolopyridine structure but only recovered starting material. In order to enhance the reactivity of this compound, it was then decided to introduce a halogen atom on the pyridine ring [11]. Thus the pyridylthiourea **13** was prepared from 2-amino-5-bromo-3-chloropyridine (**12**) [18] in 86 % yield as shown in Scheme 6. Treatment of **13** under basic conditions led, in this case, to the formation of the thiazolopyridine **14** in good yield (67 %). Palladium cross-coupling reaction with benzeneboronic acid produced then compound **15** (32 %) which, after hydrolysis, led to the target structure **4**.

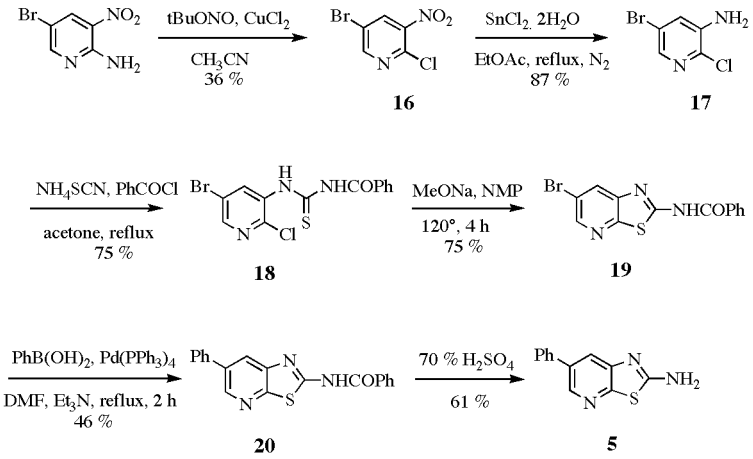
Scheme 6



The yield of the palladium cross-coupling step is unusually low for this type of reaction and optimization were undertaken. Thus the reaction was carried out in various solvents such as benzene, toluene-methanol or dimethoxyethane or with sodium carbonate as base. Various amounts of benzeneboronic acid were also used but none of these modifications improved the yield of this reaction. It appeared that a large excess of base and benzeneboronic acid is necessary to get a reasonable yield of the coupled product. A similar sequence was then used to prepare the regioisomeric thiazolopyridine **5** (Scheme 7).

First, compound **16** was prepared by a substitutive deamination process [19] starting from the commercially available 2-amino-5-bromo-3-nitropyridine, *tert*-butylnitrite and anhydrous copper (II) chloride. It was then reduced to 3-amino-5-bromo-2-chloropyridine (**17**) with tin (II) chloride dihydrate. The corresponding thiourea was then formed by the same method as previously described and **18** was obtained in 75 % yield. Subsequent cyclization was realized under basic conditions, followed by the

Scheme 7



palladium cross-coupling reaction that led to the formation of **20**, once again with a low yield (46 %). Finally **20** was hydrolyzed to **5** in 61 % yield.

Conclusion.

The thiazolopyridine derivatives described herein represent interesting targets for biological evaluation, if we consider the parent benzothiazole compounds or the heterocyclic amine PhIP (**3**). Moreover, the methodology described here can be used to prepare various analogues substituted for structure-activity relationship studies.

EXPERIMENTAL

General.

Melting points were measured using the capillary method in a Büchi apparatus B-545 and are uncorrected. Infrared spectra were obtained from a Perkin-Elmer 1600 series FTIR. Nmr spectra were recorded at 300 MHz for ^{1}H and 75 MHz for ^{13}C on a Bruker AM 300 apparatus. ^{13}C at 125 MHz were recorded on a JEOL Eclipse + 500 apparatus, using Delta program. Chemical shifts (δ) are reported in ppm and are referenced to the solvent (δ = 2.51 and 7.26 ppm). Mass spectra (ESI) were performed on a Perkin-Elmer API 150 EX spectrometer. Elemental analyses were performed by H. Kolbe Mikroanalytisches Laboratorium, Mülheim am Ruhr, Germany. All reagents were of commercial quality and were used as received. All solvents were purified by distillation or were of HPLC grade. Reactions were monitored by thin layer chromatography using Macherey-Nagel Alugram® SIL G/UV$_{254}$ aluminium plates. Separations by column chromatography were performed using 60A (40-63μm) silica. *tert*-Butylnitrite was prepared according to a literature procedure [20]. Copper (II) chloride was dried in an oven at 110 °C before use.

Aminopyridine Compounds.

2-Amino-5-bromo-3-chloropyridine (**12**).

This compound was prepared according to the procedure described in [18]. Mp (aq. CH_3OH) = 97 °C (lit [18] mp = 95 °C); ir (potassium bromide): 3465, 3273, 3140, 1622, 1467, 888, 745; ^{1}H nmr (dimethyl sulfoxide-d6): δ 8.02 (d, J = 2.1 Hz, 1H, H-6), 7.84 (d, J = 2.2 Hz, 1H, H-4), 6.53 (b, 2H, NH_2); ^{13}C nmr (dimethyl sulfoxide-d6): δ 154.7(s), 146.6(d), 138.1(d), 113.9(s), 104.1(s).

5-Bromo-2-chloro-3-nitropyridine (**16**).

Compound **16** was prepared by a procedure similar to that described in [19]. A solution of 2.5 g (24 mmol; 1.5 eq.) of *tert*-butylnitrite, 2.6 g (19.2 mmol; 1.2 eq.) of anhydrous copper (II) chloride and anhydrous acetonitrile (70 mL) was warmed to 70 °C under stirring. 2-Amino-5-bromo-3-nitropyridine (16 mmol) was then added portionwise over a period of 5 minutes to the green reaction solution. During this addition the solution turned black and nitrogen gas evolved. The mixture was heated during 2 hours and then allowed to reach room temperature. After which the reaction mixture was poured in to 100 mL of 20 % HCl, followed by extraction with ether. The organic layer was washed with 20 % HCl and dried over anhydrous Na_2SO_4. After concentration under reduced pressure, the residue was purified on a silica gel column using CH_2Cl_2 as eluent. Compound **16** was then obtained (1.35 g; 36 %) as a white solid, that could be recrystallized from hexane; mp = 67 °C (lit [21] mp = 68 °C); ir (potassium bromide): 3025, 1566, 1543, 1519, 1337, 1055, 755; ^{1}H nmr (deuteriochloroform): δ 8.69 (d, J = 2.2 Hz, 1H, H-4), 8.37 (d, J = 2.2 Hz, 1H, H-6); ^{13}C nmr (dimethylsulfoxide-d6): δ 153.8(d), 144.5(s), 140.3(s), 137.3(d), 119.1(s).

3-Amino-5-bromo-2-chloropyridine (**17**).

A solution of 200 mg (0.84 mmol) of 5-bromo-2-chloro-3-nitropyridine (**16**) and 950 mg (4.2 mmol; 5 eq.) of $SnCl_2$•$2H_2O$ in ethyl acetate(2 mL) was refluxed under nitrogen during 3 hours. After cooling to room temperature, the reaction mixture was poured into water. The resulting solid (residue from $SnCl_2$) was filtered off and washed with ethyl acetate, and the aqueous filtrate extracted by the same solvent. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and purified by silica gel column (ether/hexane 5/5). The white solid thus obtained (152 mg; 87 %) was recrystallized from water. Mp = 130 °C (lit [21°] mp = 131 °C); ir (potassium bromide): 3453, 1623, 1435, 1111, 859, 708; ^{1}H nmr (dimethyl

sulfoxide-d6): δ 7.66 (d, J = 2.2 Hz, 1H, H-6), 7.30 (d, J = 2.2 Hz, 1H, H-4), 5.89 (b, 2H NH_2); ^{13}C nmr (dimethyl sulfoxide-d6): δ 142.8(s), 135.6(d), 133.7(s), 123.1(d), 119.1(d).

N-Methylpyridylthioureas.

N-(5-Bromo-2-pyridyl),*N*'-methylthiourea (**7a**).

Compound **7a** was prepared as follows: a solution of 500 mg (2.9 mmol) of 2-amino-5-bromopyridine **6a** and 630 mg (8.7 mmol; 3 eq.) of methyl isothiocyanate in 15 mL of toluene was refluxed during 48 hours. The solution was then allowed to cool to room temperature and by this time a precipitate appeared slowly in the reaction solution that was collected by filtration and washed with ether. More substance was obtained from the filtrate by keeping it at –18 °C. Compound **7a** (496 mg; 70 %) was recrystallized from aq. ethanol; mp = 206 °C (lit [22] mp = 224 °C); ir (potassium bromide): 3214, 3151, 3088, 1596; ^{1}H nmr (dimethyl sulfoxide-d6): δ 11.05 (s, 1H, NHMe), 10.69 (s, 1H, NH), 8.30 (d, J = 2.2 Hz, 1H, H-6), 7.95 (dd, J = 8.9, 2.2 Hz, 1H, H-4), 7.10 (d, J = 8.9 Hz, 1H, H-3), 3.05 (s, 3H, Me); ^{13}C nmr (dimethyl sulfoxide-d6): δ 180.1(s), 152.3(s), 146.0(d), 141.3(d), 114.3(d), 111.7(s), 31.6(q).

N-Methyl,N'-(5-phenyl-2-pyridyl)thiourea (**7b**).

The same procedure as above was used with the following amounts: 2-amino-5-phenylpyridine (**6b**): 560 mg (3 mmol); methyl isothiocyanate: 650 mg (9 mmol; 3 eq.). **7b** was obtained with 56 % yield (410 mg) as a white solid; it was recrystallized from aq. ethanol; mp = 211 °C; ir (potassium bromide): 3203, 3144, 3026, 1591, 1573; ^{1}H nmr (dimethyl sulfoxide-d6): δ 11.49 (b, 1H, NHMe), 10.69 (s, 1H, NH), 8.51 (d, J = 2.2 Hz, 1H, H-6), 8.09 (dd, J = 8.7, 2.4 Hz, 1H, H-4), 7.31-7.71 (m, 5H, Ph), 7.24 (d, J = 8.7 Hz, 1H, H-3), 3.11 (s, 3H, Me); ^{13}C nmr (dimethyl sulfoxide-d6): δ 180.2(s), 152.8(s), 143.3(d), 137.0(d), 136.5(s), 129.5(d), 129.0(d), 127.6(d), 126.2(d), 112.5(d), 31.4(q); m/z (ESI) ($[M+H]^+$), 100 %) = 244.3.

Anal. Calcd. for $C_{13}H_{13}N_3S$ (243.33): C, 64.17; H, 5.38; N, 17.26. Found: C, 64.11; H, 5.27; N, 17.24.

N-Benzoylpyridylthioureas.

Method 1.

Benzoyl isothiocyanate was added dropwise to a stirred solution of **6a** or **6b** in aq. ethanol at room temperature. The resulting mixture was stirred for 15 minutes more and the precipitate was collected by filtration, washed with ethanol and dried under reduced pressure.

Method 2.

Benzoyl isothiocyanate was prepared *in situ*. A mixture of ammonium thiocyanate and acetone was warmed until a clear solution was obtained. Benzoyl chloride was then slowly dropped in and the resulting suspension refluxed 5 minutes. The aminopyridine dissolved in acetone was thus added and the reaction mixture was refluxed for 1 hour. After cooling to room temperature, the solution was poured into water and the resulting solid was collected by filtration, washed with water and ether and dried under reduced pressure.

N-Benzoyl-*N*'-(5-bromo-2-pyridyl)thiourea (**8a**).

Compound **8a** (312 mg; 80 %) was obtained according to Method 1 by using 200 mg (1.16 mmol) of **6a** and benzoyl isothiocyanate (0.16 mL; 1 eq.). It was recrystallized from benzene; mp = 164 °C (lit [23] mp = 164-168 °C); ir (potassium bromide): 3378, 2990, 1666, 1525, 703; ^{1}H nmr (dimethyl sulfoxide-d6): δ 13.23 (boad s, 1H, NH), 11.95 (b, 1H, NH), 8.66 (broad s, 1H, H-3), 8.59 (d, J = 2.2 Hz, 1H, H-6), 8.16 (dd, J = 8.8, 2.3 Hz, 1H, H-4), 7.98 (d, J = 7.6 Hz, 2H, Ph), 7.54-7.71 (m, 3H, Ph); ^{13}C nmr (dimethyl sulfoxide-d6): δ 178.0(s), 150.2(s), 148.9(d), 140.6(d), 133.2(d), 132.1(s), 128.6(d), 128.5(d), 117.0(d), 115.5(s). The broad signal from the H-3 atom sharpened upon heating. The desbromo analog of **8a** displayed a similar phenomenon.

N-Benzoyl-*N*'-(5-phenyl-2-pyridyl)thiourea (**8b**).

Compound **8b** (222 mg; 56 %) was prepared using Method 1, with 200 mg (1.18 mmol) of **6b** and benzoyl isothiocyanate (0.16 mL; 1 eq.). White crystals were obtained from aq. ethanol, mp = 155 °C; ir (potassium bromide): 3283, 3025,1666, 1531; ^{1}H nmr (dimethyl sulfoxide-d6): δ 13.38 (1b, 1H, NH), 11.79 (b, 1H, NH), 8.58 (m, 2H, H-3 and H-6), 8.24 (dd, J = 8.6, 2.4 Hz, 1H, H-4), 8.01 (d, J = 7.4 Hz, 2H, COPh), 7.77 (d, J = 7.4 Hz, 2H, Ph), 7.43-7.70 (m, 6H, Ph and COPh); m/z (ESI) ($[M+H]^+$, 100 %) = 334.3.

Anal. Calcd. for $C_{19}H_{15}N_3OS$ (333.41): C, 68.45; H, 4.53; N, 12.60. Found: C, 68.33; H, 4.59; N, 12.52.

N-Benzoyl-*N*'-(5-bromo-3-chloro-2-pyridyl)thiourea (**13**).

According to Method 2, the following quantities were used: 1 g (4.8 mmol) of 2-amino-5-bromo-3-chloropyridine (**12**) in 1.5 mL of acetone; 400 mg (5 mmol; 1.04 eq.) of ammonium thiocyanate and 0.6 mL (5mmol; 1.04 eq.) of benzoyl chloride in 1.5 mL of acetone. Compound **13** (1.55 g; 86 %) was recrystallized from ethanol; mp = 156 °C; ir (potassium bromide): 3155, 3026, 1666, 1502, 1155, 71; ^{1}H nmr (dimethyl sulfoxide-d6): δ 12.38 (b, 1H, NH), 11.89 (b, 1H, NH), 8.66 (d, J = 2.1 Hz, 1H, H-6), 8.59 (d, J = 2.2 Hz, 1H, H-4), 7.80 (d, J = 7.3 Hz, 2H, Ph), 7.52-7.71 (m, 3H, Ph); ^{13}C nmr (dimethyl sulfoxide-d6): δ 180.7(s), 168.1(s), 147.9(d), 147.8(s), 140.6(d), 133.3(d), 131.9(s), 129.3(s), 128.7(d), 128.5(d), 118.6(s).

Anal. Calcd. for $C_{13}H_9N_3OSBrCl$ (370.66): C, 42.13; H, 2.45; N, 11.34; S, 8.65. Found C, 42.10; H, 2.36; N, 11.22; S, 8.54.

N-Benzoyl-*N*'-(5-bromo-2-chloro-3-pyridyl)thiourea (**18**).

Compound **18** was obtained according to Method 2 by using 500 mg (2.4 mmol) of **17** in 1.5 mL of acetone; 190 mg (2.5 mmol; 1.04 eq.) of ammonium thiocyanate and 0.3 mL (2.5 mmol; 1.04 eq.) of benzoyl chloride in acetone (1 mL). Compound **18** was prepared with 75 % yield (666 mg) and was recrystallized from ethanol; mp = 177 °C; ir (potassium bromide): 3459, 3295, 1672, 1513, 679; ^{1}H nmr (dimethyl sulfoxide-d6): δ 12.77 (b, 1H, NH), 12.04 (b, 1H, NH), 8.81 (d, J = 2.3 Hz, 1H, H-6), 8.53 (d, J = 2.3 Hz, 1H, H-4), 8.01 (d, J = 7.4 Hz, 2H, Ph), 7.54-7.72 (m, 3H, Ph); ^{13}C nmr (dimethyl sulfoxide-d6): δ 180.6(s), 168.5(s), 147.5(d), 144.7(s), 138.5(d), 133.9(s), 133.4(d), 131.7(s), 128.8(d), 128.5(d), 117.8(s).

Anal. Calcd. for $C_{13}H_9N_3OSBrCl$ (370.66): C, 42.13; H, 2.45; N, 11.34; S, 8.65. Found: C, 42.24; H, 2.34; N, 11.30, S, 8.71.

Hugershoff Reaction Compounds.

General procedure: a mixture of thiourea in acetic acid was warmed until a clear solution was obtained. Bromine was then added dropwise and the resulting mixture was stirred 1 hour at room temperature. The orange solid was collected by filtration, washed with acetic acid, water and acetonitrile and dried under reduced pressure.

6-Bromo-2-methylamino-1,2,4-thiadiazolo[2,3-*a*]pyridinium Bromide (**9a**).

Compound **9a** was obtained according to the general procedure from 150 mg (0.6 mmol) of **7a** in acetic acid (4 mL) and 0.2 mL (4 mmol; 6.5 eq.) of bromine. Compound **9a** (137 mg; 70 %) was recrystallized from water; mp = 229 °C; ir (potassium bromide): 3447, 1590, 1455, 1387, 822; ^{1}H nmr (dimethyl sulfoxide-d6): δ 9.42 (d, J = 1.8 Hz, 1H, H-6), 9.30 (b, 1H, NH), 8.27 (dd, J = 9.3, 2 Hz, 1H, H-4), 7.74 (d, J = 9.2 Hz, 1H, H-3), 3.17 (d, J = 4.9 Hz, 3H, Me); ^{13}C nmr (dimethyl sulfoxide-d6): δ 171.2(s), 156.3(s), 143.8(d), 135.8(d), 118.1(d), 109.6(s), 31.3(q).

Anal. Calcd. for $C_7H_7N_3SBr_2$ (325.03): C, 25.87; H, 2.17; N, 12.93. Found: C, 25.9; H, 2.12; N, 12.84.

2-Methylamino-6-phenyl-1,2,4-thiadiazolo[2,3-*a*]pyridinium Bromide (**9b**).

Compound **9b** (178 mg; 89 %) was prepared from 150 mg (0.6 mmol) of **7b** in 4 mL of acetic acid and 0.2 mL (4 mmol; 6.5 eq.) of bromine. It was recrystallized from water; mp = 222 °C; ir (potassium bromide): 3458, 2989, 1594, 1467, 1398, 757; ^{1}H nmr (dimethyl sulfoxide-d6): δ 9.53 (d, J = 1.6 Hz, 1H, H-6); 9.39 (d, J = 4.6 Hz, 1H, NH), 8.46 (dd, J = 9.1, 1.9 Hz, 1H, H-4), 7.86 (d, J = 9.1 Hz, 1H, H-3), 7.45-7.78 (m, 5H, Ph), 3.20 (d, J = 4.9 Hz, 3H, Me); ^{13}C nmr (dimethyl sulfoxide-d6): δ 170.6(s), 155.7(s), 139.8(d), 134.1(s), 133.1(d), 117.0(d), 129.5(s), 129.4(d), 128.8(d), 126.5(d), 126.4(d), 31.2(q).

Anal. Calcd. for $C_{13}H_{12}N_3SBr$ (322.23): C, 48.4; H, 3.7; N, 13.04; S, 9.95. Found: C, 48.45; H, 3.74; N, 12.87; S, 9.77.

N-[6-Bromo-[1,2,4]thiadiazolo[2,3-*a*]pyridylidene]benzamide (**10a**).

Compound **10a** was formed by reaction between 200 mg (0.6 mmol) of **8a** and 0.2 mL (4 mmol; 6.5 eq.) of bromine in 4 mL of acetic acid; **10a** was obtained with 98 % yield (193 mg) and was recrystallized from a mixture of DMF and H_2O; mp = 246 °C; ir (potassium bromide): 3442, 3054, 1581, 1517, 1358, 721; ^{1}H nmr (dimethyl sulfoxide-d6): δ 9.45 (d, J = 1.7 Hz, 1H, H-7), 8.24-8.28 (m, 3H, H-5 and Ph), 7.83 (d, J = 9.2 Hz, 1H, H-4), 7.56-7.69 (m, 3H, Ph) ^{13}C nmr (dimethyl sulfoxide-d6): δ 177.0(s), 176.2(s), 154.6(s), 142.00(d), 135.0(d), 132.8(d), 132.7(s), 128.7(d), 119.8(d), 109.9(s).

Anal. Calcd. for $C_{13}H_8N_3OSBr$ (334.20): C, 46.72; H, 2.41; N, 12.57; S, 9.59; Br, 23.91. Found: C, 46.67; H, 2.33; N, 12.63; S, 9.46; Br, 23.85.

N-[6-Phenyl-[1,2,4]thiadiazolo[2,3-*a*]pyridylidene]benzamide (**10b**).

Compound **10b** was obtained according to the general procedure with 150 mg (0.45 mmol) of **8b** and 0.15 mL of bromine in quantitative yield. White crystals were obtained from aq. ethanol; mp = 256 °C; ir (potassium bromide): 3413, 3049, 1525, 1373, 720, 691; ^{1}H nmr (dimethyl sulfoxide-d6): δ 9.54 (d, J = 1.4 Hz, 1H, H-7), 8.53 (dd, J = 9, 1.7 Hz, 1H, H-5), 8.27 (d, J = 7.2 Hz, 2H, COPh), 8.01 (d, J = 9 Hz, 1H, H-4), 7.84 (d, J = 7.5 Hz, 2H, Ph), 7.49-7.69 (m, 6H, COPh and Ph); ^{13}C nmr (dimethyl sulfoxide-d6): 176.8(s), 154.6(s), 138.2(d), 134.8(s), 133.1(s), 132.6(d), 131.9(d), 129.6(s), 129.2(d), 128.7(d), 128.6(d), 126.7(d), 118.5(d).

Anal. Calcd. for $C_{19}H_{13}N_3OS$ (331.40): C, 68.86; H, 3.95; N, 12.68; S, 9.67. Found: C, 68.73; H, 3.90; N, 12.75; S, 9.70.

Jacobson Reaction Compounds.

General Procedure.

Potassium ferricyanide and potassium hydroxide were added to a suspension of thiourea in water at room temperature. The reaction mixture was then stirred or refluxed during the time required and the solid was collected by filtration, washed with water and dried under reduced pressure after appropriate work-up.

1-(5-Bromo-pyridin-2-yl)-3-methyl-urea (**11**).

This compound (178 mg; 31 %) was prepared according to the general procedure by using 615 mg (2.5 mmol) of **7a**, 1.9 g (5.75 mmol; 2.3 eq.) of KOH in 60 mL of H_2O. It was stirred 2.5 days at room temperature. The solid collected after filtration was purified by column of silica gel (ethyl acetate/petroleum ether 8/2) and **11** was obtained altogether with the starting material **7a** (225 mg; 37 %). The same compound **11** was also prepared by refluxing the reaction mixture 5 hours instead with a similar yield of 30 %. It was recrystallized from water; mp = 201 °C; ir (potassium bromide): 3260, 3037, 1690, 1584, 822, 626; ^{1}H nmr (dimethyl sulfoxide-d6): δ 9.32 (s, 1H, NH), 8.26 (d, J = 2.3 Hz, 1H, H-6), 7.88 (dd, J = 8.9, 2.5 Hz, 1H, H-4), 7.51 (s, 1H, NH), 7.46 (d, J = 8.9 Hz, 1H, H-3), 2.70 (s, 3H, Me); ^{13}C nmr (dimethyl sulfoxide-d6): δ 154.9(s), 152.3(s), 147.2(d), 140.4(d), 113.2(d), 110.6(s), 25.9(q).

Anal. Calcd. for $C_7H_8N_3OBr$ (230.06): C, 36.54; H, 3.50; N, 18.26. Found: C, 36.66; H, 3.42; N, 18.14.

N-[6-Bromo-[1,2,4]thiadiazolo[2,3-a]pyridylidene]benzamide (**10a**).

Compound **10a** described above, was prepared from 200 mg (0.6 mmol) of **8a**, 454 mg (1.38 mmol; 2.3 eq.) of potassium ferricyanide and 155 mg (2.76 mmol; 4.6 eq.) of KOH in 15 mL of H_2O. **10a** was produced in quantitative yield (208 mg).

Thiazolopyridine Compounds.

N-(6-Bromo-thiazolo[4,5-*b*]pyridin-2-yl)-benzamide (**14**).

A mixture of 1.5 g (4 mmol) of **13**, 432 mg (8 mmol; 2 eq.) of sodium methoxide and 10 mL of NMP was heated to 120 °C during 4 hours. It was then allowed to reach room temperature and was poured into water. The resulting pale brown solid was collected by filtration, washed with water and ether and dried under reduced pressure. More substance was obtained by extracting the previous filtrate with chloroform and evaporating to dryness the organic layer after usual work-up. **14** (893 mg) was obtained in 67 % yield. It can be recrystallized from a mixture of DMF and H_2O; mp = 328 °C; ir (potassium bromide): 3421, 3049, 2939, 1665, 1575, 1519, 1283, 695; ^{1}H nmr (dimethyl sulfoxide-d6): δ 13.25 (b, 1H, NH), 8.79 (d, J = 2.2 Hz, 1H, H-5), 8.66 (d, J = 2.2 Hz, 1H, H-7), 8.16 (d, J = 7.3 Hz, 2H, Ph), 7.56-7.70 (m, 3H, Ph); ^{13}C nmr (dimethyl sulfoxide-d6): δ 166.6(s), 162.9(s), 159.1(s), 148.1(d), 132.2(d), 131.4(s), 128.7(d), 128.4(d), 127.0(s), 113.6(s).

Anal. Calcd. for $C_{13}H_8N_3OSBr$ (334.20): C, 46.72; H, 2.41; N, 12.57; S, 9.59. Found: C, 46.67; H, 2.28; N, 12.39; S, 9.71.

N-(6-Bromo-thiazolo[5,4-*b*]pyridin-2-yl)-benzamide (**19**).

Compound **19** was obtained according to a procedure similar to the one described above. **18** (600 mg; 1.6 mmol) was heated with 173 mg (3.2 mmol; 2 eq.) of sodium methoxide in 8 mL of NMP. **19** was recrystallized from acetonitrile; mp = 250 °C; ir

(potassium bromide): 3467, 3143, 2941, 1677, 1587, 1531, 1296, 933, 704; ^{1}H nmr (dimethyl sulfoxide-d6): δ 13.18 (b, 1H, NH), 8.63 (d, J = 2 Hz, 1H, H-5), 8.48 (d, J = 2 Hz, 1H, H-7), 8.16 (d, J = 7.4 Hz, 2H, Ph), 7.57-7.73 (m, 3H, Ph); ^{13}C nmr (dimethyl sulfoxide-d6): δ 166.3(s), 159.9(s), 153.6(s), 145.8(d), 143.1(s), 133.3(d), 131.4(s), 129.6(d), 128.7(d), 128.5(d), 117.6(s).

Anal. Calcd. for $C_{13}H_8N_3OSBr$ (334.20): C, 46.72; H, 2.41; N, 12.57; S, 9.59. Found: C, 46.57; H, 2.29; N, 12.39; S, 9.71.

N-(6-Phenyl-thiazolo[4,5-*b*]pyridin-2-yl)-benzamide (**15**).

A solution of $Pd(PPh_3)_4$ (111 mg; 0.1 eq.), triethylamine (1.1 mL; 7.7 mmol; 8 eq.), benzeneboronic acid (703 mg; 5.8 mmol; 6 eq.) in 2 mL of DMF was deoxygenated during 30 minutes by bubbling N_2 in it. It was then added to a deoxygenated solution of **14** (320 mg; 0.96 mmol) and 2 mL of DMF and the resulting mixture was heated to slight reflux during 24 hours, under N_2 atmosphere. After allowing it to reach room temperature, the reaction suspension was poured into water and extracted with chloroform. The organic layer was washed with water and dried over anhydrous Na_2SO_4. After filtration, it was concentrated under reduced pressure and purified by silica gel column with ethyl acetate and hexane (5/5) as eluent. Compound **15** was thus obtained in 32 % yield (100 mg) as a white solid. Mp = 301 °C (ethyl acetate); ir (potassium bromide): 3463, 3053, 1665, 1528, 1283, 701; ^{1}H nmr (dimethyl sulfoxide-d6): δ 13.25 (b, 1H, NH), 8.89 (s, 1H, H-5), 8.81 (s, 1H, H-7), 8.18 (d, J = 7.6 Hz, 2H, COPh), 7.69 (d, J = 7.8 Hz, 2H, Ph), 7.44-7.63 (m, 6H, COPh and Ph); ^{13}C nmr (dimethyl sulfoxide-d6, 125 MHz): δ 167.0(s), 162.8(s), 160.3(s), 146.8(d), 137.8(s), 133.7(d), 132.1(s), 131.6(s), 129.7(d), 129.4(d), 129.3(d), 129.00(d), 128.4(d), 127.6(d), 126.0(s).

Anal. Calcd. for $C_{19}H_{13}N_3OS$ (331.40): C, 68.86; H, 3.95; N, 12.68; S, 9.68. Found: C, 68.95; H, 3.78; N, 12.49; S, 9.82.

N-(6-Phenyl-thiazolo[5,4-*b*]pyridin-2-yl)-benzamide (**20**).

This compound was prepared according to the procedure described for **15**, starting from the same amounts of chemicals (compound **19** was used instead). In this case, the reaction mixture was refluxed 2 hours. **20** (145 mg; 46 %) was then recrystallized from ethyl acetate; mp = 257 °C; ir (potassium bromide): 3447, 3053, 1669, 1545, 1297, 710; ^{1}H nmr (dimethyl sulfoxide-d6): δ 13.10 (b, 1H, NH), 8.84 (d, J = 1.9 Hz, 1H, H-5), 8.39 (d, J = 1.7 Hz, H-7), 8.17 (d, J = 7.4 Hz, 2H, COPh), 7.84 (d, J = 7.3 Hz, 2H, Ph), 7.44-7.73 (m, 6H, COPh and Ph).

Anal. Calcd. for $C_{19}H_{13}N_3OS$ (331.40): C, 68.86; H, 3.95; N, 12.68; S, 9.68. Found: C, 68.75; H, 3.93; N, 12.61; S, 9.55.

6-Phenylthiazolo[4,5-*b*]pyridin-2-ylamine (**4**).

Compound **15** (140 mg; 0.4 mmol) was heated to slight reflux in 2 mL of 70 % H_2SO_4 during 20 minutes. During this time, the initial white suspension turned to a brown solution. After cooling to room temperature, it was poured into water and basified by 30 % NaOH. The resulting precipitate was collected by filtration, washed with H_2O and ether and dried under reduced pressure. Compound **4** (38 mg) was produced in 40 % yield as a beige solid. It can be recrystallized from a mixture of ethyl acetate and DMF; mp = 257 °C; ir (potassium bromide): 3455, 3270, 3050, 1635, 1436, 1374, 764; ^{1}H nmr (dimethyl sulfoxide-d6): δ 8.54 (d, J = 2.2 Hz, 1H, H-5), 8.39 (d, J = 2.2 Hz, 1H, H-7), 8.01 (b, 2H, NH_2), 7.69 (d, J = 7.4 Hz, Ph), 7.35-7.51 (m, 3H, Ph); m/z (ESI) ($[M+H]^+$), 100 %) = 228.4.

Anal. Calcd. for $C_{12}H_9N_3S$ (227.29): C, 63.41; H, 3.99; N, 18.49. Found: C, 63.70; H, 4.12; N, 18.18.

6-Phenylthiazolo[5,4-*b*]pyridin-2-ylamine (**5**).

Compound **5** (48 mg; 61 %) was prepared according to a procedure similar to the one described for **4**, starting from 115 mg (0.35 mmol) of compound **20**. It was recrystallized from a mixture of ethyl acetate and hexane; mp = 207 °C; ir (potassium bromide): 3455, 3287, 3084, 1641, 1523, 1362, 754; ^{1}H nmr (dimethyl sulfoxide-d6): 8.41 (d, J = 2.1 Hz, 1H, H-5), 7.87 (m, 3H, H-7 and NH_2), 7.73 (d, J = 7.1 Hz, 2H, Ph), 7.41-7.52 (m, 3H, Ph).

Anal. Calcd. for $C_{12}H_9N_3S$ (227.29): C, 63.41; H, 3.99; N, 18.49; S, 14.11. Found: C, 63.42; H, 4.12; N, 18.36; S, 14.06.

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