

Francesco Guerrera*, Maria Angela Siracusa, Benedetto Tornetta,
and Ennio Bousquet

Istituto Chimica Farmaceutica e Tossicologica,
Università di Catania, 95125 Catania, Italy

Pasquale Agozzino and Liliana LaMartina

Istituto Chimica Farmaceutica e Tossicologica,
Università di Palermo, 90123 Palermo, Italy

Received July 21, 1983

A facile and convenient synthesis of the title compounds is described, using as starting materials the 2-nitro-3-aminothieno[2,3-*b*]pyridines. Mass spectral data of the above mentioned compounds are briefly discussed.

J. Heterocyclic Chem., **21**, 587 (1984).

It is generally acknowledged that the imidazole nucleus is a common structural feature of polycondensed heterocyclic molecules endowed with biological activity. Recent reports in the literature have described the synthesis of 1*H*-pyrazolo[3',4':4,5]thieno[2,3-*b*]pyridine [1] which possesses antirhinoviral activity. In view of this fact and our interest in thieno[2,3-*b*]pyridine compounds [2,3,4] it seemed worthwhile to synthesize 1*H*-imidazo[3',4':4,5]thieno[2,3-*b*]pyridine derivatives with eventual perspectives for examining their possible biological action.

The synthesis of pyridothienoimidazole derivatives was initiated with 2-nitro-3-aminothieno[2,3-*b*]pyridine [5] (see Figure 1) because the natural precursor, 2,3-diaminothi-

eno[2,3-*b*]pyridine has not been isolated.

Compounds **1** were acetylated with acetic anhydride and acetyl chloride which gave the 2-nitro-3-diacetamidothieno[2,3-*b*]pyridines **2**. Alkaline hydrolysis at room temperature produced the 2-nitro-3-acetamidothieno[2,3-*b*]pyridines **3**. The latter were transformed into 2,3-diacetamidothieno[2,3-*b*]pyridines **4'** by catalytic hydrogenation (Pd/C) in the presence of an acetic acid-acetic anhydride mixture. Products **4'** as well as their formyl derivatives were obtained in good yields by direct catalytic reduction of compounds **1** in acetic acid-acetic anhydride or formic acid medium.

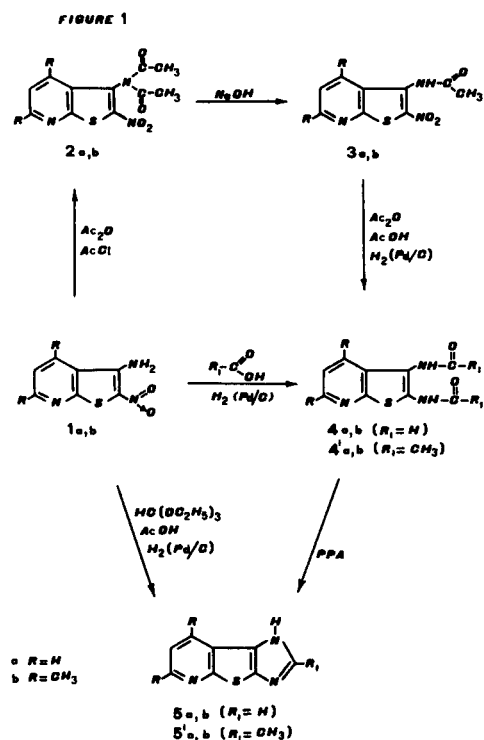
Moreover, the formyl derivatives can be prepared in the absence of hydrogen taking advantage of the reducing action of formic acid in the presence of Pd/C. The 2,3-diacylamino compounds **4** were cyclized by heating at 160° in PPA for 4 hours and gave the expected pyridothienoimidazoles **5**.

A single step reaction was studied in order to arrive at a direct synthesis of pyridothienoimidazole derivatives. This procedure was carried out by catalytic reduction of compounds **1** in the presence of triethyl orthoformate and acetic acid. The yields of this reaction were greater than 60%. Unfortunately, the same reaction in the presence of triethyl orthoacetate produced a dark mixture which gave very poor yields of the products. However, the 1*H*-2-methylimidazo[3',4':4,5]thieno[2,3-*b*]pyridine and the 2,3-diacetamido derivatives could be observed by tlc.

Catalytic reduction under high hydrogen pressure decreased the reaction time but did not improve the yields of the products, in all the reactions described in this study.

Analytical and spectroscopic data (ir, ¹H-nmr and ms) of all products are in agreement with the described structures.

In particular, the mass spectra of 2,3-diacetyl amino derivatives **4'** are characterized by the presence of intense peaks corresponding to primary loss of CH₂CO from acetyl



derivatives. The latter ions lose the acyl radicals, followed by HCN elimination.

The mass spectra of the new ring system compounds shows some characteristic fragmentation: in fact in the unsubstituted compounds **5a,b** the main peaks correspond to the whole loss of HCN (m/z 148), H_2CN (m/z 147), $2HCN$ (m/z 121) and C_2H_2NS ($-H_2CN$, $-CS$; m/z 104). In the other cyclic derivatives **5'a,b** an identical trend is observed; methyl compounds lose CH_3CN instead of HCN, while the presence of substituents on the pyridine ring produces the obvious mass shift. In addition, the M-H ions are present in all the methyl substituted compound spectra whereas the primary CH_3 loss is observed only for the 6,8-dimethyl derivatives.

EXPERIMENTAL

Melting points were determined on a Büchi 510 apparatus and are uncorrected. Elemental analysis was performed on a C. Erba, elemental analyzer Model 1106. The ir spectra were determined using a Perkin-Elmer Spectrophotometer 281. The 1H -nmr spectra were recorded in TFA on a Perkin-Elmer R32 spectrometer operating at 90 MHz. Chemical shifts are reported in ppm from TMS as an internal standard and are given in δ units. Mass spectra are run on a Jeol JMS 015G-2 double focusing mass spectrometer with a 10KV accelerating voltage and 75 eV electronic beam energy.

3-Amino-2-nitrothieno[2,3-*b*]pyridine (**1a,b**)

Twenty mmoles of 3-cyanopyridine-2-thiol derivatives was dissolved in 30 ml of dimethylformamide and 20 mmoles of bromonitromethane was added. The mixture was stirred while 10 ml of 20% aqueous potassium hydroxide was added. After 2 hours the mixture was poured in ice-water. The products were collected and crystallized (yields \approx 80%).

Compound **1a**.

This compound had mp 267-269° (from acetic acid); ir (potassium bromide): 3400 3290 cm^{-1} (NH_2), 1575, 1390 cm^{-1} (NO_2).

Anal. Calcd. for $C_7H_5N_3O_2S$: C, 43.07; H, 2.58; N, 21.53. Found: C, 42.95; H, 2.56; N, 21.29.

Compound **1b**.

This compound had mp 266-268° (from acetic acid) (lit [5] 246-248°); ir (potassium bromide): 3440, 3320 cm^{-1} (NH_2), 1550, 1370 cm^{-1} (NO_2).

3-Diacetamido-2-nitrothieno[2,3-*b*]pyridine (**2a,b**)

Twenty mmoles of **1a,b** were refluxed with 50 ml of acetic anhydride and 0.5 ml of acetyl chloride for 2 hours. Upon cooling, the products were precipitated with water, filtered and crystallized (yields \approx 80%).

Compound **2a**.

This compound had mp 105-106° (from cyclohexane); ir (potassium bromide): 1740 and 1710 cm^{-1} ($2 \times C=O$), 1560, 1370 cm^{-1} (NO_2).

Anal. Calcd. for $C_{11}H_{13}N_3O_4S$: C, 47.32; H, 3.25; N, 15.05. Found: C, 47.29; H, 3.27; N, 14.97.

Compound **2b**.

This compound had mp 172-174° (from cyclohexane); ir (potassium bromide): 1740 and 1710 cm^{-1} ($2 \times C=O$), 1535, 1370 cm^{-1} (NO_2).

Anal. Calcd. for $C_{13}H_{15}N_3O_4S$: C, 50.81; H, 4.26; N, 13.68. Found: C, 50.85; H, 4.24; N, 13.59.

3-Acetamido-3-nitrothieno[2,3-*b*]pyridine (**3a,b**)

Ten mmoles of **2a,b** were dissolved in 10 ml of ethanol and 10 ml of 10% aqueous potassium hydroxide. The mixture was stirred for 15

minutes and the solution was acidified with acetic acid. The products which separated, were filtered and crystallized (yields \approx 80%).

Compound **3a**.

This compound had mp 195-197° (from benzene); ir (potassium bromide): 3300 cm^{-1} (NH), 1680 cm^{-1} ($C=O$), 1575, 1380 cm^{-1} (NO_2).

Anal. Calcd. for $C_8H_7N_3O_3S$: C, 45.56; H, 2.98; N, 17.72. Found: C, 45.23; H, 2.95; N, 17.51.

Compound **3b**.

This compound had mp 200-201° (from benzene); ir (potassium bromide): 3260 cm^{-1} (NH), 1680 cm^{-1} ($C=O$), 1550, 1370 cm^{-1} (NO_2).

Anal. Calcd. for $C_{11}H_{11}N_3O_3S$: C, 49.81; H, 4.18; N, 15.84. Found: C, 49.77; H, 4.19; N, 15.79.

2,3-Diformamidothieno[2,3-*b*]pyridine (**4a,b**)

Method A.

Five mmoles of **1a,b** were mixed with 250 mg of palladium on carbon. Air was displaced with nitrogen and 97% formic acid (30 ml) was added. The mixture was hydrogenated for 12 hours. The solution was filtered and evaporated to dryness *in vacuo*, and crystallized (yields \approx 75%).

Method B.

To a mixture of 5 mmoles of **1a,b** and 3 g of 10% palladium on carbon, under nitrogen, 97% formic acid (50 ml), was added. The reaction was stirred for 1 hour and heated at 70° for 5 hours. The solution was filtered and evaporated to dryness *in vacuo*. The residue was treated with water, filtered and crystallized (yields \approx 70%).

Compound **4a**.

This compound had mp 253-254° (from acetonitrile); ir (potassium bromide): 1670 and 1640 cm^{-1} ($2 \times C=O$); nmr: δ 7.90 (dd, $J_{5,6} = 5.8$ Hz and $J_{4,5} = 7.9$ Hz, 1H, C(5)-H), 8.40-8.80 (m, 4H, C(4)-H, C(6)-H and $2 \times HC=O$), 9.20 and 10.20 (2 bs, each 1H, $2 \times NH$).

Anal. Calcd. for $C_8H_7N_3O_2S$: C, 48.86; H, 3.18; N, 18.99. Found: C, 48.90; H, 3.22; N, 19.02.

Compound **4b**.

This compound had mp 265-267° (from water); ir (potassium bromide): 1680 and 1655 cm^{-1} ($2 \times C=O$); nmr: δ 2.95 (s, 6H, $2 \times CH_3$), 7.60 (s, 1H, C(5)-H), 8.75 and 8.78 (2s, each 1H, $2 \times HC=O$), 9.20 and 10.20 (s and bs, each 1H, $2 \times NH$).

Anal. Calcd. for $C_{11}H_{11}N_3O_2S$: C, 53.01; H, 4.44; N, 16.86. Found: C, 52.97; H, 4.35; N, 16.85.

2,3-Diacetamidothieno[2,3-*b*]pyridine (**4'a,b**)

Five mmoles of **1a,b** were dissolved in a mixture of acetic anhydride (15 ml) and acetic acid (60 ml) and hydrogenated over 5% palladium on carbon (200 mg) for 12 hours. The mixture was filtered, and the filtrate was evaporated to dryness *in vacuo*. The residue was treated with water, filtered and crystallized (yields \approx 75%). These products were also obtained analogously from **3a,b** (see Figure 1).

Compound **4'a**.

This compound had mp 262-263° (from water); ir (potassium bromide): 1685 and 1645 cm^{-1} ($2 \times C=O$); nmr: δ 2.50 and 2.55 (2s, each 3H, $2 \times COCH_3$), 8.03 (dd, $J_{5,6} = 5.7$ Hz and $J_{4,5} = 7.9$ Hz, 1H, C(5)-H), 8.75 (m, 2H, C(4)-H and C(6)-H), 9.15 and 10.15 (2s, each 1H, $2 \times NH$).

Anal. Calcd. for $C_{11}H_{11}N_3O_4S$: C, 53.01; H, 4.44; N, 16.86. Found: C, 52.95; H, 4.44; N, 16.75.

Compound **4'b**.

This compound had mp 258-260° (from ethyl acetate); ir (potassium bromide): 1690 and 1670 cm^{-1} ($2 \times C=O$); nmr: δ 2.50 and 2.55 (2s, each 3H, $2 \times COCH_3$), 2.90 (s, 6H, $2 \times CH_3$), 7.55 (s, 1H, C(5)-H), 9.05 and 9.85 (2s, each 1H, $2 \times NH$).

Anal. Calcd. for $C_{13}H_{15}N_3O_4S$: C, 56.3; H, 5.45; N, 15.15. Found: C, 56.00; H, 5.35; N, 15.03.

1*H*-Imidazo[3',4':4,5]thieno[2,3-*b*]pyridine (**5a,b**); (**5'a,b**).

Method A.

Five mmoles of **4a,b** or **4'a,b** were placed with PPA and shaken at a temperature of 160° for 4 hours. Upon cooling, water was added to the mixture which was neutralized with sodium hydrogen carbonate. The product which separated, was filtered and crystallized (yields \cong 70%).

Method B (for **5a,b**).

Five mmoles of **1a,b** were dissolved in a mixture of ethyl orthoformate (15 ml) and acetic acid (60 ml) and 5% palladium on carbon (200 mg) was added. The mixture was hydrogenated at room temperature for 12 hours. The catalyst was removed by filtration and the filtrate was evaporated. The residue was treated with water and was filtered and crystallized (yields for **5a** 60%, for **5b** 70%).

Compound **5a**.

This compound had mp 209-210° (from ethyl acetate); nmr: δ 8.30 (dd, $J_{6,7} = 5.7$ Hz, $J_{7,8} = 8.1$ Hz, 1H, C(7)-H), 9.15 (d, $J_{6,7} = 5.7$ Hz, 1H, C(6)-H), 9.35 (s, 1H, C(2)-H), 9.45 (d, $J_{7,8} = 8.1$ Hz, 1H, C(8)-H).

Anal. Calcd. for $C_8H_5N_3S$: C, 54.84; H, 2.86; N, 23.98. Found: C, 54.65; H, 2.89; N, 23.89.

Compound **5b**.

This compound had mp 320-322° (from dimethylformamide); nmr: δ 3.05 (s, 3H, CH_3 at C(6)), 3.20 (s, 3H, CH_3 at C(8)), 7.90 (s, 1H, C(7)-H), 9.35 (s, 1H, C(2)-H).

Anal. Calcd. for $C_{10}H_9N_3S$: C, 59.09; H, 4.46; N, 20.67. Found: C, 59.12; H, 4.43; N, 20.55.

Compound **5'a**.

This compound had mp 244-245° (from water); nmr: δ 3.12 (s, 3H, CH_3), 8.30 (dd, $J_{6,7} = 5.8$ Hz and $J_{7,8} = 8.1$ Hz, 1H, C(7)-H), 9.20 (d, $J_{6,7} = 5.8$ Hz, 1H, C(6)-H), 9.35 (d, $J_{7,8} = 8.1$ Hz, 1H, C(8)-H).

Anal. Calcd. for $C_8H_7N_3S$: C, 57.12; H, 3.72; N, 22.20. Found: C, 57.12; H, 3.67; N, 22.12.

Compound **5'b**.

This compound had mp 280-281° (from acetonitrile); nmr: δ 3.00, 3.06 and 3.10 (3s, each 3H, $3 \times CH_3$), 7.85 (s, 1H, C(7)-H).

Anal. Calcd. for $C_{11}H_{11}N_3S$: C, 60.81; H, 5.10; N, 19.34. Found: C, 60.72; H, 5.00; N, 19.25.

Acknowledgement.

We thank Mr. S. Di Marco for technical assistance.

REFERENCES AND NOTES

- [1] E. C. Hermann and J. G. Whitney, European Patent Application 4,319; *Chem. Abstr.*, **92**, 1110122 (1980).
- [2] B. Tornetta, F. Guerrera and G. Ronsisvalle, *Ann. Chim. (Rome)*, **64**, 833 (1974).
- [3] F. Guerrera, M. A. Siracusa and B. Tornetta, *Farmaco Ed. Sci.*, **31**, 21 (1976).
- [4] B. Tornetta, M. A. Siracusa, G. Ronsisvalle and F. Guerrera, *Gazz. Chim. Ital.*, **108**, 57 (1978).
- [5] R. Niess and H. Eilingsfeld, German Patent 2,241,717; *Chem. Abstr.*, **80**, 146133 (1974).