Concerning the Preparations of Some Pyridylimidazothiazole Derivatives

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The preparations of some 4-pyridylimidazo[2,1-*b*]thiazole and -imidazo[5,1-*b*]thiazole derivatives are described. In some of the cyclizations to form the imidazothiazole ring systems, trifluoroacetic anhydride, the dehydration reagent employed, participated in the reaction leading to products bearing a trifluoromethyl or trifluoroacetyl substituent.

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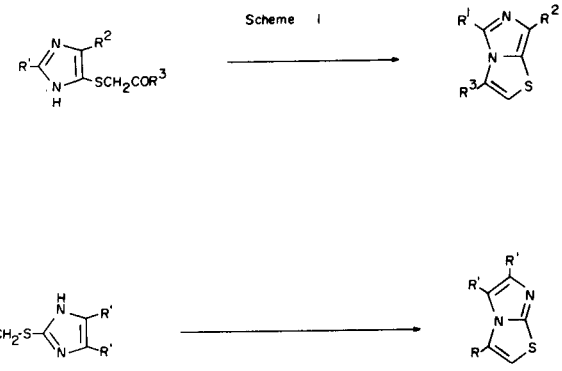
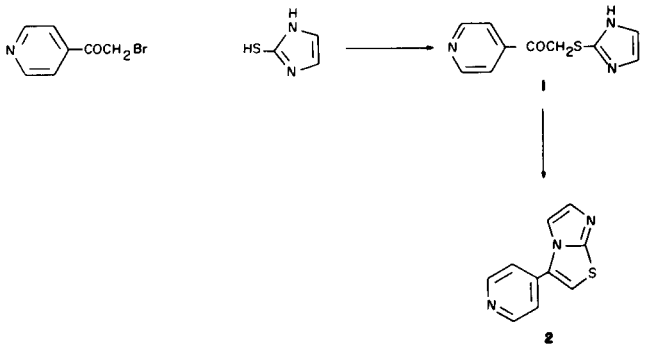
As part of a medicinal chemistry program it was of interest to prepare some imidazo[2,1-*b*]thiazole and imidazo-[5,1-*b*]thiazole derivatives, bearing 4-pyridyl substituents. While the imidazo[2,1-*b*]thiazole system is quite well represented in the literature, a much smaller number of imidazo[5,1-*b*]thiazoles have been reported. A general method of preparation for compounds of either class is the cyclization of a suitably substituted β-oxoethylthioimidazole with strong dehydrating reagents such as phosphorus oxychloride (2) (Scheme 1).

Scheme 1



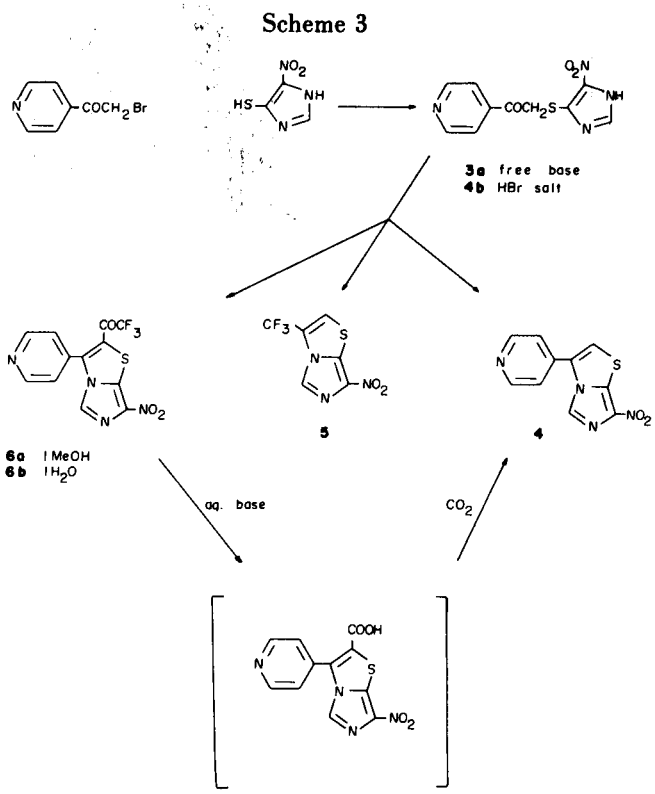
The phosphorus oxychloride procedure proved to be unsatisfactory for the cyclizaiton of the (imidazolylthioacetyl)pyridine **1** to 3-(4-pyridyl)imidazo[2,1-*b*]thiazole **2** and an alternative cyclization procedure was sought. A solution to the problem appeared to have been found when it was observed that treating the dihydrobromide salt of **1** with trifluoroacetic anhydride for 4 hours at room temperature gave rise cleanly to **2**; which was isolated in satisfactory yield as the dihydrochloride.

Scheme 2



However, when this procedure was applied to the preparation of another pyridylimidazo[5,1-*b*]thiazole derivative **4** the reaction sequence did not follow a simple course; instead the trifluoroacetic anhydride participated in the formation of by-products. Reaction of 4-bromoacetylpyridine hydrobromide with 5-nitro-4-imidazolethiol afforded **3** which was isolated as the hydrobromide. When the reaction of this compound wtih trifluoroacetic anhydride was studied on a small scale it was found to be transformed slowly (six days under reflux) to a mixture of two com-

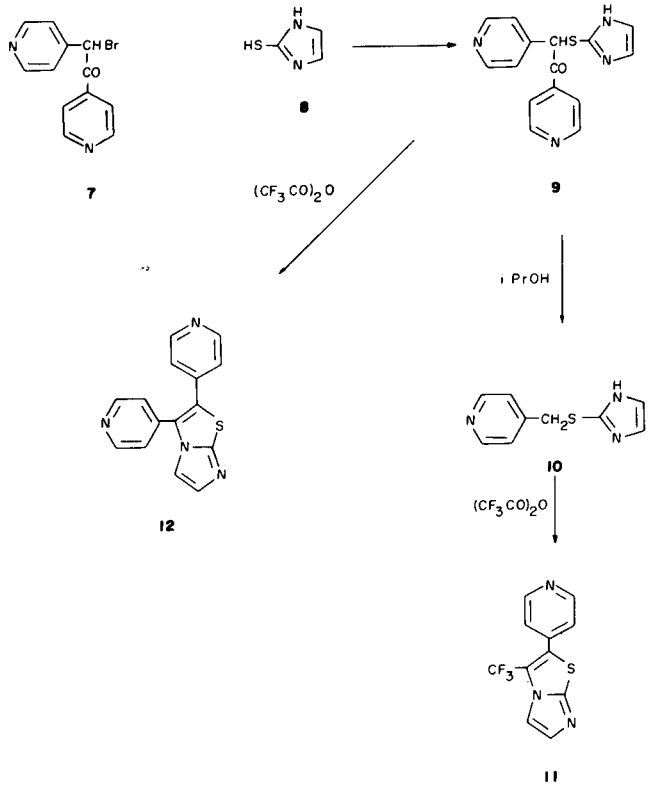
Scheme 3



pounds which were easily separated by virtue of their very different solubilities in dimethylformamide, and shown to be **4** and **5**. However, when the reaction was scaled up, a much more difficultly-separable mixture of three compounds was obtained. The reason for the discrepancy in the two experiments was realized when the third compound was isolated and characterized as **6**. This compound is very susceptible to base, presumably undergoing a haloform reaction and a subsequent facile decarboxylation to give **4**. Thus in the small scale experiment **6** could have been transformed completely to **4** as the *p*H of the mixture was being adjusted, while in the large run the transformation was incomplete. The mechanism of the formation of **6** has not been investigated except that it has been shown that prolonged treatment of **4** with trifluoroacetic anhydride does not give **6**, in the way, for example, that an electron-rich system such as azulene can be trifluoroacetylated (3). There is a possibility that **4** is formed exclusively *via* **6**. Presumably the reduced nucleophilicity of the nitroimidazole moiety of **3** reduces the rate of the desired cyclization, thus permitting side reactions to predominate.

A different problem was encountered when the synthesis of the di-(4-pyridyl)imidazothiazole **12** was attempted. Reaction of 2-mercaptoimidazole with 2-bromo-1,2-di-(4-pyridyl)ethanone dihydrobromide in boiling isopropanol (the same conditions used for the preparation of **1** gave a product, **10**, lacking an isonicotinoyl moiety, presumably due to solvolysis of the initial condensation product. Compound **10** contains a very reactive methylene group and it condenses readily with trifluoroacetic anhydride to yield the imidazo[2,1-*b*]thiazole derivative **11**. The desired dipyridyl compound **12** was obtained in rather low overall yield by condensing **7** and **8** in an aprotic solvent, tetramethylurea, and treating the crude product with trifluoroacetic anhydride.

Scheme 4



EXPERIMENTAL

Melting points (uncorrected) were determined in a Thomas Hoover capillary melting point apparatus. The ir spectra were recorded with a Perkin-Elmer 157 spectrometer and the nmr spectra were recorded using a Varian A60A spectrometer with TMS as internal standard. Microanalyses were performed by Organic Microanalyses Laboratories (Dr. C. Daessle) and mass spectra were provided by Morgan Schaffer Corporation, both of Montreal.

4-(2-Imidazolylthioacetyl)pyridine Dihydrobromide (**1**).

A mixture of 4-(bromoacetyl)pyridine hydrobromide (4) (1.55 g, 5.5 mmoles), 2-mercaptoimidazole (5) (570 mg, 5.8 mmoles) and 2-propanol (50 ml) was heated under reflux for 2 hours. After cooling the reaction mixture to room temperature, the solid was filtered and dried, affording 1.704 g (82%), mp 224° dec, of **1**. The salt was recrystallized from methanol/acetone from which it separated in rosettes of needles, mp 221-222° dec; ir (potassium bromide): ν max 1720, 1580, 1070, 800 cm^{-1}; nmr (DMSO-d_6): δ 9.27 (d, 2H, J = 6 Hz, α-pyridyl-H), 8.40 (d, 2H, J = 6 Hz, β-pyridyl-H), 7.89 (s, 2H, imidazolyl-H), 5.33 (s, 2H, CH_2).

Anal. Calcd. for $C_{10}H_9N_3OS{\cdot}2HBr$: C, 31.52; H, 2.91; Br, 41.94; N, 11.03; S, 8.42. Found: C, 31.77; H, 2.83; Br, 42.17; N, 11.25; S, 8.38.

3-(4-Pyridyl)imidazo[2,1-*b*]thiazole Dihydrochloride (**2**).

A mixture of **1** (4.00 g, 10.5 mmoles) and trifluoroacetic anhydride (50 ml) was stirred at room temperature for 4 hours and then evaporated using a rotary evaporator. The residual syrup was dissolved in water (25 ml) and the solution was basified with 10*N* sodium hydroxide thereby liberating the free base as a pinkish solid, 1.684 g (79%), mp 221-223°. The compound crystallized from acetonitrile in colourless needles, mp 230-232°; ir (potassium bromide): ν max 3105-3030, 1600, 1134, 680; nmr (DMSO-d_6): δ 8.99 (d of d, 2H, J = 6 Hz, J′ = 1 Hz, α-pyridyl-H), 8.28 (d, 1H, J = 1 Hz, imidazolyl-H), 8.00 and 7.93 (m, 3H, β-pyridyl-H and imidazolyl-H), 7.56 (t, 1H, J ~ 1 Hz, thiazolyl-H).

Treatment of the base with hydrogen chloride in ethanol afforded the dihydrochloride, mp 298-305° dec.

Anal. Calcd. for $C_{10}H_7N_3S{\cdot}2HCl$: C, 43.81; H, 3.31; Cl, 25.86; N, 15.33; S, 11.69. Found: C, 44.20; H, 3.30; Cl, 25.87; N, 15.42; S, 11.86.

4-(4(5)-Nitroimidazol-5(4)-ylthioacetyl)pyridine Hydrobromide (**3b**).

A mixture of 4(5)-mercapto-5(4)-nitroimidazole (6) (3.20 g, 10 mmoles) 4-bromoacetylpyridine hydrobromide (62.0 g, 10 mmoles) and isopropanol (2.2 ℓ) was heated under reflux for 2 hours with efficient stirring. The mixture was allowed to cool to room temperature and the solid was collected and washed with propanol, 70 g (93%). The salt can be recrystallized from water (~40 ml/g) and then has mp 232-236° dec; ir (potassium bromide): ν max 1735, 1369, 1061; nmr (DMSO-d_6): δ 10 (broad s, exchangeable H), 9.31 (d of d, 2H, J = 6 Hz, J′ ~ 1 Hz, α-pyridyl-H), 8.49 (d of d, 2H, J = 6 Hz, J′ = 1 Hz, β-pyridyl-H), 8.13 (s, 1H, imidazolyl-H), 5.19 (s, 2H, CH_2). The integration of the CH_2 signal was a little low suggesting partial enolization or perhaps slow exchange with the solvent.

Anal. Calcd. for $C_{10}H_8N_4SO_3{\cdot}HBr$: C, 34.79; H, 2.63; Br, 23.15; N, 16.23; S, 9.29. Found: C, 34.56; H, 2.63; Br, 22.85; N, 16.15; S, 9.39.

The free base **3a** was obtained by treating a suspension of **3b** in water with sodium bicarbonate. The orange solid was collected, washed, and dried.

Reaction of 4-(4(5)-Nitroimidazol-5(4)-yl-thioacetyl)pyridine With Trifluoroacetic Anhydride.

A mixture of **3a** (195.1 g, 0.738 mole) and trifluoroacetic anhydride (1.685 ℓ) was stirred under reflux for 6 days. Excess trifluoroacetic anhydride was distilled off and the residue was treated with 10% sodium carbonate solution to *p*H 7. The solid was collected, washed with water and dried. This three-component mixture was boiled with methanol (3 ℓ) and filtered. From the filtrate a yellow solid **6a** crystallized, 17.9 g, mp 180-183°. Further recrystallization of the solid from methanol raised the mp to 184-186°; nmr (DMSO-d_6/deuterium oxide): δ 8.97 (d, of d, 2H, J = 6 Hz, J′ ~ 1 Hz, α-pyridyl-H), 8.13 (s, 1H, imidazolyl-H), 7.82 (d of d, 2H, J = 6 Hz, J′ ~ 1 Hz, β-pyridyl-H), 3.25 (s, 3H, OCH_3); ms: m/e = 342.

Recrystallization of the compound from dimethylformamide/acetonitrile resulted in loss of methanol from the material, and gave 7-nitro-2-trifluoroacetyl-3-(4-pyridyl)imidazo[5,1-*b*]thiazole hydrate **6b** of mp 191-193° dec; ir (potassium bromide): ν max 3570, 3025 (sharp spike on a large broad band), 1622, 1599, 1535, 1185 cms^{-1}. The nmr spectrum was identical to that above except for the asbsence of the OCH_3 signal.

Anal. Calcd. for $C_{12}H_5F_3N_4O_3S{\cdot}H_2O$: C, 40.00; H, 1.96; F, 15.82; N, 15.55; S, 9.00. Found: C, 40.40; H, 1.75; F, 15.74; N, 15.99; S, 8.68.

On allowing the methanol mother liquors to stand, more solid crystallized out slowly, 59.9 g, mp 223-225°. Recrystallization of this solid from methanol afforded 3-trifluoromethyl-7-nitroimidazo[5,1-*b*]thiazole **5**, mp 223-225°; ir: 3140, 3050, 1532, 1278, 1096; nmr (DMSO-d_6): δ 8.77 (s, 1H, thiazole-H), 8.68 (m, 1H, imidazole-H); ms: m/e = 237.

Anal. Calcd. for $C_6H_2F_3N_3SO_2$: C, 30.39; H, 0.85; F, 24.03; N, 17.72; S, 13.52. Found: C, 30.47; H, 0.77; F, 23.99; N, 17.79; S, 13.44.

Concentration of methanol mother liquors gave 32 g of a mixture.

The fraction that was insoluble in boiling methanol was recrystallized from dimethylformamide to yield 7-nitro-3-(4-pyridyl)imidazo[5,1-*b*]thiazole **4**, 12.5 g, mp 302-204° dec. The pure compound crystallized from dimethylformamide has mp 307-309°; ir (potassium bromide): ν max 3142, 3030, 1532, 1388; nmr (DMSO-d_6): δ 8.99 (m, 2H, α-pyridyl-H), 8.85 (s, 1H, thiazolyl-H), 8.20 (s, 1H, imidazole-H), 7.91 (m, 2H, β-pyridyl-H).

Anal. Calcd. for $C_{10}H_6N_4O_2S$: C, 48.77; H, 2.45; N, 22.75; S, 13.02. Found: C, 48.78; H, 2.40; N, 22.76; S, 12.94.

Evaporation of the DMF mother liquors gave 12.5 g of crude material.

Conversion of 7-Nitro-2-trifluoroacetyl-3-(4-pyridyl)imidazo[5,1-*b*]thiazole to 7-Nitro-3-(4-pyridyl)imiazol[5,1-*b*]thiazole.

A suspension of **6a** (500 mg, 1.34 mmoles) in 2*N* sodium hydroxide (5 ml) was stirred at room temperature for 10 minutes, then the *p*H was adjusted to 5 with 2*N* hydrochloric acid. The solid was filtered off, washed and dried, providing 339 mg of **4** identical by ir, mp, and mixed mp to the compound isolated earlier.

2-(4-Pyridylthio)imidazole Dihydrobromide (**10**).

A suspension of 2-mercaptoimidazole (1.22 g, 12 mmoles), 2-bromo-1,2-di-(4-pyridyl)ethanone dihydrobromide (5.27 g, 12.0 mmoles) and 2-propanol (180 ml) was stirred under reflux for 2 hours. The mixture was allowed to stand at room temperature for 48 hours and the crude product was collected 4.79 g. This solid could not be recrystallized satisfactorily and so an analtyical sample was obtained by preparative plate chromatography of the free base (silica gel developed with 1:50 ammonium hydroxide:2-propanol) followed by reconversion of the pure base to the dihydrobromide by treatment with hydrogen bromide in ethanol/ether, mp 220-225° with darkening; ir (potassium bromide): ν max 2910, 2800, 1638, 1609, 1582, 773; nmr (DMSO-d_6): δ 8.98 (d, 2H, J = 6 Hz, α-pyridyl-H), 8.00 (d, 2H, J = 6 hz, β-pyridyl-H), 7.80 (s, 2H, imidazolyl-H), 4.81 (s, 2H, CH_2), exchangeable protons at 11.5.

Anal. Calcd. for $C_9H_9N_3S{\cdot}2HBr$: C, 30.61; H, 3.14; Br, 45.26; S, 9.08. Found: C, 30.45; H, 3.17; Br, 45.53; S, 9.23.

2-(4-Pyridyl)-3-trifluoromethylimidazo[2,1-*b*]thiazole Dihydrochloride (**11**).

A mixture of crude **10** (4.90 g, 13.9 mmoles) and trifluoroacetic anhydride (50 ml) was stirred at room temperature overnight. Excess anhydride was distilled off and the residue was treated with 10% sodium carbonate solution and extracted with ethyl acetate. The base isolated from the ethyl acetate extract was dissolved in 2-propanol and a slight excess of hydrogen chloride in ethanol was added, affording **11**, 2.23 g (47%), mp 248-250°. Pure **11** recrystallized from ethanol had mp 250-251°; ir: ν max 3450 (broad) 3000-3200 (broad multiplet), 1502, 1198 cm^{-1}; nmr (acetonitrile-d_3): δ 8.70 (d, 2H, J = 6 Hz, α-pyridyl-H), 7.70 (s, 1H, imidazolyl-H), 7.43 (d, 2H, J = 6 Hz, β-pyridyl-H), 7.34 (s, 1H, imidazolyl-H); ms: m/e = 269.

Anal. Calcd. for $C_{11}H_6F_3N_3S{\cdot}2HCl$: C, 38.61; H, 2.36; Cl, 20.12. Found: C, 38.37; H, 2.80; Cl, 20.30.

(1,2-Di-(4-pyridyl)-2-oxoethylthio)imidazole (**9**).

The bromo ketone **7** (2.20 g, 5.0 mmoles) was suspended in tetramethylurea (25 ml) and 2-mercaptoimidazole (0.625 mg, 6.1 mmoles) was added. The mixture was stirred at room temperature for 3 days. Dry ether was added to precipitate the crude product which was filtered quickly and used immediately because of its hygroscopic nature.

2,3-Di-(4-pyridyl)imidazo[2,1-*b*]thiazole Trihydrochloride Dihydrate (**12**).

Crude **9** from the above reaction was added to trifluoroacetic anhydride (40 ml) and the mixture was stirred at room temperature for 3 days. The solid was partitioned between 10% sodium carbonate solution and ethyl acetate. The extract was dried (magnesium sulfate) and evaporated to dryness. The crude base was dissolved in 2-propanol and a slight excess of ethanolic hydrogen chloride was added. Addition of a little ether completed the precipitation of the title compound. The hydrochloride was recrystallized from ethanol, 140 mg (35%), mp 298-300° dec; ir: ν max 3410 (broad), 3060 (broad), 1643, 1609, 1597; nmr (DMSO-d_6): of the free base δ 8.93 (d of d, 2H, J = 6 Hz, J′ ~ 1 Hz, α-pyridyl-H), 7.85 (d, 1H, J ~ 1 Hz, imidazolyl-H), 7.73 (d of d, 2H, J = 6 Hz, J′ ~ 1 Hz, β-pyridyl-H), 7.50 (d, 1H, J ~ 1 Hz, imidazolyl-H), 7.40 (d of d, 2H, J = 6 Hz, J′ ~ 1 Hz, β-pyridyl-H).

Anal. Calcd. for $C_{15}H_{10}N_4S{\cdot}3HCl{\cdot}2H_2O$: C, 42.52; H, 4.04; Cl, 25.11; N, 13.22; S, 7.57. Found: C, 42.22; H, 4.43; Cl, 25.25; N, 12.98; S, 7.82.

REFERENCES AND NOTES

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