# Synthetic and Mechanistic Studies on the Preparation of Pyridyl-Substituted Imidazothiazoles†

Ivan Lantos,* Kerry Gombatz, Michael McGuire, Lendon Pridgen, James Remich, and Susan Shilcrat

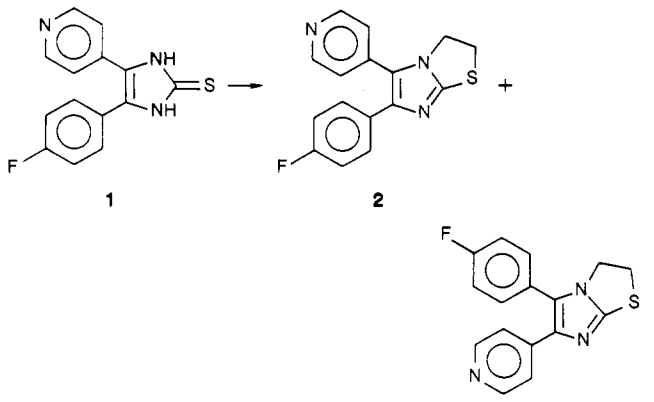
*Division of Chemical Research and Development, Smith Kline and French Laboratories, King of Prussia, Pennsylvania*

*Received December 23, 1987*

A new method is presented for the introduction of the 4′-pyridyl substituent into 6-aryl-2,3-dihydroimidazo[2,1-*b*]thiazoles. The method involves treatment of the imidazothiazolines with the reactive complex of pyridine and ethyl chloroformate and oxidative deethyl carboxylation of the dihydropyridine adducts formed. Sulfur in refluxing mesitylene was found most suitable for the latter reaction, but chromium trioxide in pyridine or KtBuO and air were also effective.

Synthetic studies previously carried out in our laboratories have uncovered a class of imidazo[2,1-*b*]thiazolines possessing potent antiarthritic properties.[1] Of particular significance was compound **2** bearing the 4-pyridyl substituent in the 5-position and the 4-fluorophenyl residue in the 6.[1b]

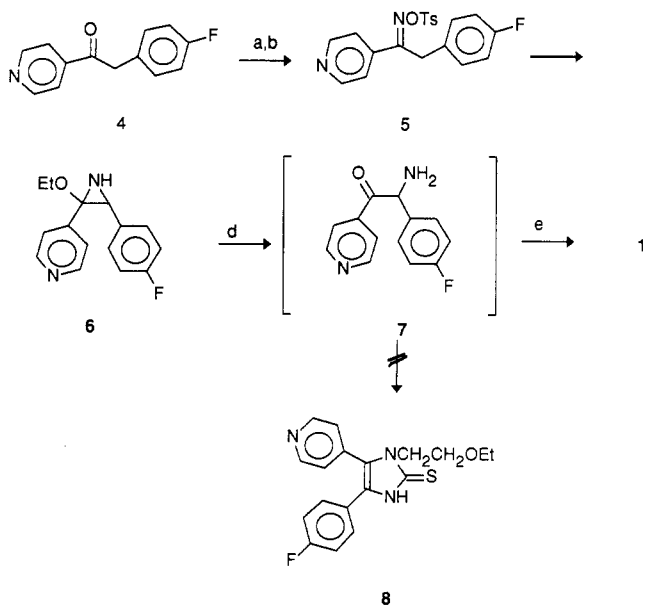
Our previous route to this compound, relying on the well-established[2] intermediate imidazo thione **1**, afforded a 1:1 mixture of isomers of **2** and **3** and thus was unsuitable for the preparation of **2** in quantities required for toxicity studies. The discovery of a new, selective route was required. As part of this effort we examined the feasibility of an alternative route, shown in Scheme I, on the basis of the intermediacy of α-amino ketone **7**. This route, utilizing the Neber[3] rearrangement of oxime tosylates, was also used by Ciba-Geigy researchers[4] for the preparation of similar systems. The three-step sequence provided the previously utilized imidazothione precursor **1**, in a state of purity suitable for further conversion to **2** and **3** as was done previously. However, attempts to condense the amino ketone **7** with functionalized isothiocyanate failed to afford the regioselectively substituted imidazothione **8**. Only products resulting from self-condensation of **7** were observed.



**1** **2** **3**

Extensive efforts were then made to improve the product ratio of **2** and **3** formed during the elaboration of the thiazoline nucleus. These were only marginally successful; the reaction of **1** with dibromoethane under acidic, instead of the standard basic conditions, resulted in a 60:40 mixture of **2**:**3**. Stepwise conversion of the thione to the hydroxyethylene derivative with bromoethanol and subsequent cyclization by acid treatment offered no improvement in the regioselectivity of the cyclization.

**Scheme I**[a]



**4** **5** **6** **7** **8**

[a] Reagents: (a) $NH_2OH$/pyridine; (b) TsCl; (c) EtOK/EtOH; (d) HCl; (e) KCNS; (f) $EtOCH_2CH_2NCS$.

We then turned to the possibility of introducing the pyridyl substituent into the preassembled 6-arylimidazo[2,1-*b*]thiazoline heterocycle **9b** (Scheme II), since these compounds could be readily prepared either by the condensation of α-haloacetophenones with aminothiazoline[5] or alternatively by a new approach starting with 5-aminoimidazo[2,1-*b*]thiazolines.[6] Examination of the reactivity of **9b** (Ar = 4-fluorophenyl) toward electrophilic reagents indicated that the molecule possesses a high degree of nucleophilic character,[7] and it appeared therefore,

† This paper is dedicated to Prof. J. T. Edward of McGill University, Montreal, on the occasion of his 66th birthday.

(1) (a) Bender, P. E.; Hill, D. T.; Offen, P. H.; Razgaitis, K.; Lavanchy, P.; Stringer, O. D.; Sutton, B. M.; Griswold, D. E.; DiMartino, M. J.; Walz, D. T.; Lantos, I.; Ladd, C. B. *J. Med. Chem.* **1985**, *28*, 1169. (b) Lantos, I.; Bender, P. E.; Razgaitis, K.; Sutton, B. M.; Dimartino, M. J.; Griswold, D. E.; Walz, D. T. *J. Med. Chem.* **1984**, *27*, 72.

(2) Markova, Yu-V.; Kuz'mina, K. K.; Peresleni, E. M.; Shchukina, M. N. *Zh. Org. Khim.* **1965**, *1*, 1475.

(3) Neber, P. W.; Friedolsheim, A. V. *Justus Liebigs Ann. Chem.* **1926**, *449*, 109. Neber, P. W.; Huh, G. *Ibid.* **1935**, *515*, 283.

(4) Ciba-Geigy AG. Bicyclic thiadiaza compounds and their use as medicaments. Brit. UK Pat. Appl. 2,039,882; *Chem. Abstr.* **1981**, *95*, 43104*r*.

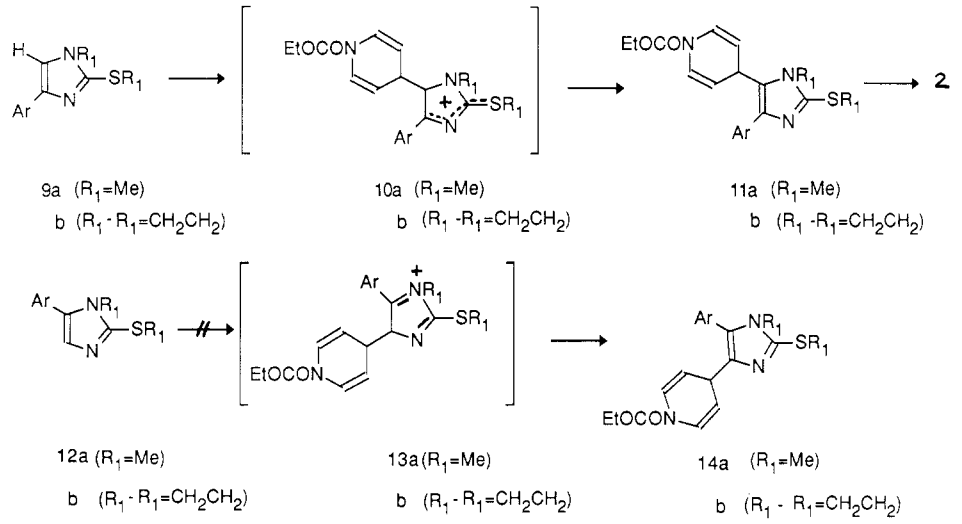
(5) Raeymaekers, A. H. M.; Allewijn, F. T. N.; Vandenberk, J.; Demoen, P. J. A.; Van Offenwert, T. T. T.; Jansen, P. A. J. *J. Med. Chem.* **1966**, *9*, 545.

(6) Lantos, I.; McGuire, M. *Heterocycles* **1986**, *24*, 991.

(7) Specifically, the compound undergoes brominations readily and with yields in excess of 85%.

0022-3263/88/1953-4223$01.50/0 © 1988 American Chemical Society

**Scheme II**




that it might also react with a reagent containing an electrophilic pyridine. On the basis of the elegant work of Comins,[8] Akiba,[8] and others,[9] which exploits the reactivity of the pyridine/ethyl chloroformate complex with nucleophilc species, it appeared that the reactivity of various imidazothiazolines with this reagent was also worthy of consideration. Accordingly, the pyridine–ethyl chloroformate complex was prepared and added to a solution of **9b** (Ar = 4-fluorophenyl) in methylene chloride and pyridine at 0–5 °C; aqueous workup furnished the desired dihydropyridine adduct **11b** (Ar = 4-fluorophenyl) in 50–60% yield. After considerable experimentation we found the best procedure to prepare this compound to be the slow addition of ethyl chloroformate to an ice-cold solution of the imidazo[2,1-*b*]thiazoline in a mixture of methylene chloride and pyridine. This procedure consistently afforded the dihydropyridine adduct in 80–85% yield.

Conversion of **11b** (Ar = 4-fluorophenyl) to our original target was readily carried out by several oxidative[9,11] methods: sulfur[10] in a hydrocarbon solvent boiling at or above 160 °C, potassium *tert*-butoxide and air, or chromium trioxide in pyridine. From each of these reactions crystalline **2** was obtained in excellent yield. In fact, the sequence proceeding from imidazothiazoline **9b** (Ar = 4-fluorophenyl) to **2** was found to be extremely versatile and economical for the synthesis of kilogram quantities of the compound.

A number of 6-aryl-imidazo[2,1-*b*]thiazolines were investigated under the standard conditions of adduct formation to probe the effect of the 4-substituent in the aryl group. As shown in Table II, the reaction was found to proceed with imidazolines bearing both electron-donating and -withdrawing substituents (i.e. 4-methoxy vs 4-cyano) in the aryl group, although the reactions were much slower in the latter case. Only the *p*-nitrophenyl compound failed to undergo the reaction. From competition studies the relative order of reactivity was found to be MeO > H > Cl. It was also of interest to find that treatment of the adducts **11b** with hot HCl smoothly reversed the reaction and resulted in the isolation of the starting imidazothiazolines **9b**.

To further explore the nature of the reaction, isomeric dimethyl imidazoles **9a** (Ar = 4-fluorophenyl) and **12a** (Ar = 4-fluorophenyl) and imidazothiazole **12b** (Ar = 4-fluorophenyl) were synthesized by various unambiguous methods, and their behavior in the reaction was investigated. A surprisingly high degree of chemoselectivity was observed, i.e., while the compounds of the **9** structural type readily underwent dihydropyridine adduct formation, those with the **12** pattern of substitution did not.

On the basis of the results of these studies, we view the presently described reaction as an electrophilic substitution with the cation **10** as an intermediate. This intermediate is stabilized by the fully extended conjugation involving the sulfur, as shown on Scheme II, to a larger degree of **10** than is the analogous cationic intermediate **13**.

Synthetic studies exploring the scope of this reaction with other heterocyclic electrophiles are ongoing, and these will be reported in due course.

## Experimental Section

All melting points were measured on a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian EM360L spectrophotometer and are reported in ppm downfield from internal $Me_4Si$. IR spectra were taken, unless stated otherwise, in KBr pellets and recorded on a Perkin-Elmer Model 283 spectrophotometer.

**Preparation of 1-(4-Pyridyl)-2-(4-fluorophenyl)ethanone (4).** A mixture of methyl isonicotinate (20.55 g, 0.15 mol) and (*p*-fluorophenyl)acetonitrile (20.25 g, 0.15 mol) was added to a solution of sodium ethoxide (15.3 g, 0.22 mol) in 75 mL of ethanol. The reaction was heated to reflux for 2 h. The solution was poured into an ice–water mixture and was acidified to pH 3.0 with 12 N HCl. The product, 1-(4-pyridyl)-2-cyano-2-(4-fluorophenyl)-ethanone (present mostly as the enol) precipitated out of the reaction mixture and was dried (mp 228–30 °C, 87% yield). The crude cyano ketone (30.0 g, 0.125 mol) was refluxed in 90 mL of 48% aqueous HBr for 13 h. The mixture was cooled, made basic by the addition of concentrated $NH_3$ solution, and was then extracted with ethyl acetate. The combined organic extracts were washed with brine and dried over anhydrous $MgSO_4$. The solution was filtered, and the solvent was removed at reduced pressure to give the desired ketone (11.8 g, 44% yield). The product was purified by crystallization from hexane, mp 70–71.5 °C: IR 1694, 1616, 1601, 1517, 809, 799 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 4.23 (2 H, s, $CH_2$), 6.73–7.35 (4 H, m, Ar), 7.57–7.82 (2 H, m, Ar), 8.58–8.87 (2 H, Ar). Anal. Calcd for $C_{13}H_{10}FNO$: C, 72.55; H, 4.68; N, 8.83;

(8) Comins, D. L.; Mantlo, N. B. *Tetrahedron Lett.* **1983**, *24*, 3683. Comins, D. L.; Abdullah., A. H. *J. Org. Chem.* **1982**, *47*, 4315. Akiba, K.; Iseki, Y.; Wada, M. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1994. Akiba, K.; Nishihara, Y.; Wada, M. *Tetrahedron Lett.* **1983**, *24*, 5269. Akiba, K. *Tetrahedron Lett.* **1982**, *23*, 3935 and references cited.

(9) Dondoni, A.; Dall'Occo, T.; Galliani, G.; Mastellari, A.; Medici, A. *Tetrahedron Lett.* **1984**, *25*, 3637. We thank one of the referees for bringing this work to our attention.

(10) Lyle, R. E.; Comins, D. L. *J. Org. Chem.* **1976**, *41*, 3250.

(11) For the use of chloranil in these oxidations, see: Comins, D. L. *Tetrahedron Lett.* **1983**, *24*, 2807.

Table I. 6-Arylimidazo[2,1-*b*]thiazolines (9b)[a]

| R (Ar = RPh) | yield, % | mp, °C | IR, cm$^{-1}$ | $^1$H NMR ($CDCl_3$), δ |
|---|---|---|---|---|
| H | 55[b] | 149–50 | 1470, 1370, 1185, 735, 685 | 3.47–4.23 (4 H, m, $CH_2CH_2$), 6.97–7.87 (5 H, m, Ar), 7.13 (1 H, s, imid) |
| 4-methoxy | 75[f] | 164–5 | 1550, 1460, 1240, 1025, 835, 745 | 3.53–4.27 (4 H, m, $CH_2CH_2$), 3.82 (3 H, s, $CH_3O$), 6.7–7.03 (2 H, m, Ar), 7.07 (1 H, s, imid), 7.43–7.80 (2 H, m, Ar) |
| 4-fluoro | 80[d] | 154–5 | 1590, 1470, 1210, 830, 750 | 3.47–4.30 (4 H, m, $CH_2CH_2$), 6.77–7.27 (2 H, m, Ar), 7.12 (1 H, s, imid), 7.43–7.83 (2 H, m, Ar) |
| 4-cyano | 60[e] | 201–2 | 2210, 1605, 1170, 835, 755 | 3.63–4.38 (4 H, m, $CH_2CH_2$), 7.43–7.92 (4 H, m, Ar), 7.32 (1 H, s, imid) |
| 4-chloro | 77[f] | 161–2 | 1545, 1420, 1190, 820, 750 | 3.53–4.30 (4 H, m, $CH_2CH_2$), 7.07–7.77 (4 H, m, Ar), 7.13 (1 H, s, imid) |
| 4-methyl | 90[g] | 225–6[h] | 1460, 1365, 1175, 810, 740 | 2.32 (3 H, s, $CH_3$), 3.47–4.23 (4 H, m, $CH_2CH_2$), 6.97–7.32 (2 H, m, Ar), 7.08 (1 H, s, imid), 7.42–7.75 (2 H, m, Ar) |
| 4-nitro | 89[i] | 230–1 | 1575, 1490, 1455, 1320, 900, 845, 740 | 3.75–4.45 (4 H, m, $CH_2CH_2$), 7.79–8.35 (4 H, m, Ar), 8.02 (1 H, s, imid)[l] |
| 3-methoxy | 80[j] | 119–20 | 1605, 1475, 1370, 1270, 1160, 1040, 745 | 3.48–4.20 (4 H, m, $CH_2CH_2$), 3.78 (3 H, s, $CH_3$), 6.57–6.90 (1 H, m, Ar), 7.00–7.35 (3 H, m, Ar), 7.12 (1 H, s, imid) |
| 3-chloro | 40[k] | 271–2[h] | 1600, 1470, 1370, 1190, 785, 745 | 3.57–4.30 (4 H, m, $CH_2CH_2$), 7.00–7.80 (4 H, m, Ar), 7.20 (1 H, s, imid) |

[a] Satisfactory elemental analyses were obtained for all compounds. Crystallization solvents are as follows. [b] Ethanol–hexane. [c] Acetone–hexane. [d] Ethanol. [e] Acetonitrile–hexane. [f] Ethanol–hexane. [g,h] Crystallized from water and melting point taken as the HBr salt. [i] Methyl ethyl ketone. [j] Ethanol–hexane. [k,h] Crystallized from ethanol and melting point taken as the HBr salt. [l] Taken in DMSO-$d_6$.

F, 6.51. Found: C, 72.24; H, 4.73; N, 8.72; F, 6.32.

**Preparation of 1-(4-Pyridyl)-2-(4-fluorophenyl)ethanone Oxime.** A solution of **4** (21.5 g, 100 mol), sodium acetate trihydrate (61.2 g, 449 mol), and hydroxylamine hydrochloride (22.8 g, 328 mmol) in 250 mL of 1:1 methanol–water was refluxed for 1 h. The solution was cooled, and the precipitated crystals were collected by filtration and dried overnight to obtain (19.5 g, 85% yield) the desired oxime, mp 192–3 °C: IR 1598, 1506, 1225, 973 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$) δ 4.30 (2 H, s, $CH_2$), 6.90–7.50 (4 H, m, Ar), 7.56–7.77 (2 H, m, Ar), 8.47–8.70 (2 H, m, Ar). Anal. Calcd for $C_{13}H_{11}FN_2O$: C, 67.83; H, 4.82; N, 12.17. Found: C, 67.79; H, 4.85; N, 12.17.

**Preparation of 1-(4-Pyridyl)-2-(4-fluorophenyl)-1-[(tolylsulfonyl)imino]ethane (5).** The oxime (9.89 g, 43.0 mmol) was dissolved in 50 mL of dry pyridine, and *p*-toluenesulfonyl chloride (11.44 g, 60.0 mmol) was added with cooling. The solution was stirred for 5 h at 55 °C and poured into an ice–water mixture. The precipitate was isolated by filtration, washed with water, and dried. Upon recrystallization from ethanol–hexane, a 76% yield (12.55 g) of the desired product was obtained, mp 128.5–129.5 °C: IR 1511, 1370, 1192, 1176, 830, 760 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$) δ 2.40 (3 H, s, $CH_3$), 4.27 (2 H, s, $CH_2$), 6.90–7.30 (4 H, m, Ar), 7.33–7.70 (4 H, m, Ar), 7.73–8.03 (2 H, m, Ar), 8.50–8.77 (2 H, m, Ar). Anal. Calcd for $C_{20}H_{17}FN_2O_3S$: C, 62.49; H, 4.46; N, 7.29; S, 8.34. Found: C, 62.68; H, 4.49; N, 7.31; S, 8.52.

**Preparation of 1-(4-Pyridyl)-1-ethoxy-2-(4-fluorophenyl)aziridine (6).** A freshly prepared solution of potassium ethoxide (2.65 g, 31.5 mmol) in 25 mL of ethanol was added dropwise to a chilled solution of **5** (9.6 g, 25.0 mmol) in 50 mL of ethanol. The reaction mixture was stirred at ambient temperature for 0.5 h, ethyl ether (50 mL) was added, and the mixture was stirred for an additional 0.5 h. The suspension was filtered, and the filtrate was concentrated to yield the aziridine (5.5 g) in 86% yield. The crude product was crystallized from hexane, mp 124–125 °C: IR 3140, 1600, 1500, 1410, 1215, 1055, 825 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 1.17 (3 H, t, $J$ = 7.0 Hz, $OCH_2CH_3$), 1.70–2.13 (1 H, br s, NH), 3.50 (2 H, q, $J$ = 7.5 Hz, $OCH_2CH_3$), 3.75 (1 H, m, Ar, CH), 6.57–7.40 (6 H, m, Ar), 8.30–8.57 (2 H, m, Ar). Anal. Calcd for $C_{15}H_{15}FN_2O$: C, 69.75; H, 5.85; N, 10.85. Found: C, 69.92; H, 5.94; N, 10.92.

**Preparation of 4-(4-Pyridyl)-5-(4-fluorophenyl)-imidazole-2-thione (1).** A solution of **6** (10.32 g, 40.0 mmol) in 100 mL of ethyl acetate was treated with 10% aqueous hydrochloric acid. The aqueous phase was concentrated to dryness at reduced pressure. The residue was dissolved in 90 mL of water and treated with potassium thiocyanate (7.77 g, 40.0 mmol). After being refluxed for 2 h, the hot solution was poured into 5% aqueous sodium bicarbonate solution. The resultant precipitate was collected by filtration, washed with ethanol and acetone, and dried to obtain a 91% (9.86 g) yield of the desired product: mp >375 °C; IR 1603, 1545, 1230, 1005, 830, 545 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$ + $CF_3COOH$) δ 7.10–8.00 (6 H, m, Ar), 8.53–8.83 (2 H, m, CHNCH).

**Preparation of 6-(Aryl)-2,3-dihydroimidazo[2,1-*b*]thiazoles (9b).** The phenacetyl halides (50 mmol, Aldrich) and 2-aminothiazoline (50 mmol, Aldrich) were heated in ethanol (375 mL) at reflux temperature for 1 h. The solution was cooled to 0–5 °C in an ice bath, and the crystalline intermediate was isolated by filtration. It was suspended in 50 mL of water, and the reaction mixture was heated to reflux for 2 h. Cooling the solution in an ice bath gave the crystalline hydrogen halide salt of the desired imidazo[2,1-*b*]thiazoline, which was collected by filtration. The salt was partitioned between 5% aqueous $NaHCO_3$ and chloroform, and the organic solution was dried over anhydrous $MgSO_4$. The organic solvent was removed at reduced pressure, and the residual solid was recrystallized to furnish the crystalline **9b** listed in Table I.

**Preparation of 5-[1-(Ethoxycarbonyl)-1,4-dihydro-4-pyridyl]-6-arylimidazo[2,1-*b*]thiazolines (11b).** Imidazo[2,1-*b*]thiazoline **9b** (3 mmol) was dissolved in 10 mL of methylene chloride and 1.2 mL (15 mmol) of pyridine. The solution was cooled to 0–5 °C, and ethyl chloroformate (10 mmol) was slowly added. The reaction was allowed to warm to ambient temperature overnight. Whenever a TLC assay indicated the presence of unreacted starting material, the reaction mixture was cooled to 0–5 °C, and a second portion of pyridine and ethyl chloroformate, 10 and 5 mmol, respectively, were added. This process was continued until unreacted starting material no longer remained. The reaction was poured into water, and the organic solution was washed with saturated brine and dried over anhydrous $MgSO_4$. The organic solvents were removed in vacuo, and the residual oil product was purified by flash chromatography on silica gel. The crystalline products and solvents of crystallization are listed in Table II.

**Preparation of 6-(4-Fluorophenyl)-2,3-dihydro-5-(4-pyridyl)imidazo[2,1-*b*]thiazole (2).** The precursor dihydropyridine adduct **11b** (Ar = 4-fluorophenyl) (185.5 g, 0.5 mol) was dissolved in 400 mL of mesitylene, and sulfur (16 g, 0.5 mol) was added. The solution was heated to reflux temperature, resulting in rapid gas evolution and formation of a volatile liquid, which was distilled from the reaction mixture. Heating was discontinued after 1.5–2 h, and the solution was allowed to cool to ambient temperature. The crystalline product was collected by filtration and recrystallized from 1-propanol, furnishing a 92% yield of material identical in all respects with the compound obtained by our previous method,[1b] mp 190–192 °C: IR 1650, 1510, 1220, 1165, 845 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 3.68–4.38 (4 H, m, $CH_2CH_2$), 6.77–7.68 (6 H, m, Ar), 8.52–8.73 (2 H, m, Pyr). Alternatively, precursor **11b** (Ar = 4-fluorophenyl) (10.0 g, 27.0 mmol) was dissolved in 100 mL of *tert*-butyl alcohol, and potassium *tert*-butoxide (9.06 g, 80.0 mmol) was added. The solution was heated to reflux in an oxygen-enriched atmosphere for 2 h. The product

Table II. 6-Arylimidazo[2,1-*b*]thiazolines (11b)[a]

| R (Ar = RPh) | yield, % | mp, °C | IR ($cm^{-1}$, $CHCl_3$) | $^1H$ NMR ($CDCl_3$), δ |
|---|---|---|---|---|
| H | 85[b] | 161.5–162.5 | 2980, 1720, 1685, 1310, 1120, 975 | 1.33 (3 H, t, $J$ = 6.5 Hz, $CH_3$), 3.56–4.53 (6 H, m, $OCH_2$, $CH_2CH_2$), 4.56–5.07 (3 H, m, 3 CH), 6.77–7.12 (2 H, m, 2 CH), 7.15–7.67 (5 H, m, Ar) |
| 4-methoxy | 69[b] | 114–115 | 2970, 1720, 1685, 1335, 1310, 975 | 1.33 (3 H, t, $J$ = 6.5 Hz, $CH_3$), 3.80 (3 H, s, $OCH_3$), 3.57–4.52 (6 H, m, $OCH_2$, $CH_2CH_2$), 4.52–5.03 (3 H, m, 3 CH), 6.73–7.13 (4 H, m, Ar), 7.23–7.57 (2 H, m, 2 CH) |
| 4-fluoro | 86[c] | 143–144 | 2975, 1675, 1300, 1115, 970 | 1.33 (3 H, t, $J$ = 6.5 Hz, $CH_3$), 3.53–4.50 (6 H, m, $OCH_2$, $CH_2CH_2$), 4.53–5.03 (3 H, m, 3 CH), 6.77–7.27 (4 H, m, Ar), 7.28–7.67 (2 H, m, 2 CH) |
| 4-cyano | 49[b] | 173–174 | 2215, 1710, 1690, 1310, 1210, 975 | 1.37 (3 H, t, $J$ = 7.0 Hz, $CH_3$), 3.60–4.58 (6 H, m, $OCH_2$, $CH_2CH_2$), 4.60–5.03 (3 H, m, 3 CH), 6.77–7.13 (2 H, m, Ar), 7.33–7.80 (4 H, m, 2 CH, Ar) |
| 4-chloro | 61[b] | 176–177 | 2980, 1720, 1685, 1320, 1295, 960 | 1.35 (3 H, t, $J$ = 6.5 Hz, $CH_3$), 3.56–4.50 (6 H, m, $OCH_2$, $CH_2CH_2$), 4.50–5.00 (3 H, m, 3 CH), 6.78–7.10 (2 H, m, Ar), 7.15–7.55 (4 H, m, 2 CH, Ar) |
| 4-methyl | 76[b] | 123–124 | 2975, 1710, 1680, 1305, 1120, 970 | 1.30 (3 H, t, $J$ = 7.0 Hz, $CH_3$), 2.32 (3 H, s, $CH_3$), 3.50–4.47 (6 H, m, $OCH_2$, $CH_2CH_2$), 4.50–4.97 (3 H, m, 3 CH), 6.70–7.60 (6 H, m, 2 CH, Ar) |
| 3-methoxy[d] | 61[b] | 110–111 | 2980, 1725, 1690, 1340, 1315, 980 | 1.32 (3 H, t, $J$ = 7.0 Hz, $CH_3$), 3.80 (3 H, s, $OCH_3$), 3.48–4.48 (6 H, m, $OCH_2$, $CH_2CH_2$), 4.55–5.00 (3 H, m, 3 CH), 6.63–7.45 (6 H, m, 2 CH, Ar) |
| 3-chloro | 54[b] | 128–129 | 2980, 1730, 1695, 1380, 1340, 1325, 980 | 1.35 (3 H, t, $J$ = 7.0 Hz, $CH_3$), 3.58–4.52 (6 H, m, $OCH_2$, $CH_2CH_2$), 4.53–5.07 (3 H, m, 3 CH), 6.73–7.62 (6 H, m, 2 CH, Ar) |

[a] Satisfactory elemental analyses were obtained for all compounds except as noted. Crystallization solvents are as follows. [b] Ethyl acetate–hexane. [c] 2-Propanol. [d] Molecular weight supported by exact mass, no elemental analyses.

was isolated by neutralization with 5 N HCl and extraction with chloroform. The chloroform extract was concentrated at reduced pressure, and the crystalline product was collected by filtration. recrystallization from 1-propanol furnished the desired compound in 85% yield.

**Preparation of 1-Methyl-2-(methylthio)-4-(4-fluorophenyl)imidazole (9a, Ar = 4-fluorophenyl).** A solution of 2-amino-*p*-fluoroacetophenone hydrochloride[12] (85.3 g, 0.45 mol) and potassium thiocyanate (174.9 g, 1.8 mol) in 400 mL of 10% aqueous hydrochloric acid was heated to reflux for 2 h. Upon cooling, the product 4-(4-fluorophenyl)imidazole-2-thione precipitated from solution and was collected by filtration. The thione was partitioned between 5% aqueous $NaHCO_3$ solution and methylene chloride, and the organic solution was washed with water and brine and dried with anhydrous $MgSO_4$. Evaporation of the solvent furnished the solid imidazolethione in 52% yield. A solution of the thione (9.7 g, 50.0 mmol) in 220 mL of 2 N NaOH was treated with dimethyl sulfate (16.6 mL, 175 mmol), and stirring was maintained for 65 h. The aqueous solution was decanted, and the oily residue was dissolved in chloroform and washed with water and brine, and after drying with anhydrous $MgSO_4$, the solution was concentrated at reduced pressure. Purification of the product was effected by flash chromatography on silica gel with ethyl acetate solvent. The compound was recrystallized from hexane, mp 70–72 °C: IR 1515, 1490, 1455, 1210, 1135, 835 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 2.57 (3 H, s, $SCH_3$), 3.53 (3 H, s, $NCH_3$), 6.78–7.23 (2 H, m, Ar), 7.50–7.85 (2 H, m, Ar), 7.05 (1 H, s, imid); exact mass calculated for $C_{11}H_{11}FN_2S$ 222.063, found 222.063.

**Preparation 1-Methyl-2-(methylthio)-5-(4-fluorophenyl)imidazole (12a, Ar = 4-fluorophenyl).** A mixture of 2-amino-*p*-fluoroacetophenone hydrochloride[12] (4.74 g, 25.0 mmol) and methyl isothiocyanate (1.70 mL, 25.0 mmol) in 40 mL of toluene was treated with triethylamine (3.50 mL, 25.0 mmol) and heated at reflux for 18 h. The reaction mixture was allowed to cool to ambient temperature and was partitioned between water and chloroform. The organic layer was washed with water and brine and was dried over anhydrous $MgSO_4$. Evaporation of the solvent at reduced pressure furnished crude 1-methyl-5-(4-fluorophenyl)imidazole-2-thione (3.87 g, 74%). The crude material (3.33 g, 16.0 mmol) was suspended in 50 mL of dry DMF under a blanket of nitrogen and was treated with NaH (60% oil, 0.72 g, 18.0 mmol). After being stirred for 20 min at room temperature, iodomethane (1.25 mL, 20.0 mmol) was added, and stirring was maintained for an additional 18 h. The reaction mixture was quenched into a mixture of ice–water, and the precipitated product was collected by filtration, dried, and recrystallized from hexane to obtain a 54% yield (1.93 g) of purified compound, mp 86.5–88.5 °C: IR ($CHCl_3$) 2970, 1480, 1235, 835 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 2.63 (3 H, s, $SCH_3$), 3.52 (3 H, s, $NCH_3$), 6.97–7.53 (4 H, m, Ar), 7.07 (1 H, s, imid). Anal. Calcd for $C_{11}H_{11}FN_2S$: C, 59.44; H, 4.99; N, 12.60; F, 8.55; S, 14.42. Found: C, 59.65; H, 4.94; N, 12.53; F, 8.61; S, 14.51.

**Preparation of 5-(4-Fluorophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (12b, Ar = 4-fluorophenyl).** A mixture of 2-amino-*p*-fluoroacetophenone hydrochloride[12] (1.90 g, 10.0 mmol) and 2-bromoethyl isothiocyanate (1.66 g, 10.0 mmol) in 25 mL of toluene was treated with triethylamine (1.01 g, 10.0 mmol) and heated at reflux for 20 h with a Dean–Stark trap to remove the water azeotrope. The reaction mixture was cooled to ambient temperature and washed with 5% aqueous $NaHCO_3$, and the mixture was extracted with chloroform. The organic solution was washed with water and brine, dried over anhydrous $MgSO_4$, and evaporated to a residual oil. The oil was heated at 100 °C (0.15 Torr), furnishing the desired product in 39% yield, which was recrystallized from ethyl acetate–hexanes, mp 158–160 °C: IR 1505, 1450, 1230, 840, 810 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 3.58–4.43 (4 H, m, $CH_2CH_2$), 6.83–7.53 (4 H, m, Ar), 7.05 (1 H, s, imid); exact mass calcd for $C_{11}H_9FN_2S$ 220.047, found 220.048.

**Preparation of 1-Methyl-2-(methylthio)-4-(4-fluorophenyl)-5-(1-carbethoxy-1,4-dihydro-4-pyridyl)imidazole (11a, Ar = 4-fluorophenyl).** This compound was prepared from the corresponding **9a** in 70% yield with use of conditions similar to those used for **11a**. The product was recrystallized from ethyl acetate–hexane, mp 125.5–126.5 °C: IR 1710, 1690, 1305, 1210, 1135, 935 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.30 (3 H, t, $J$ = 7.0 Hz, $CH_3$), 2.57 (3 H, s, $SCH_3$), 3.60 (3 H, s, $NCH_3$), 4.27 (2 H, q, $J$ = 7.0 Hz, $OCH_2$), 4.57–4.97 (3 H, 3 CH), 6.70–7.67 (6 H, m, Ar, 2 CH). Anal. Calcd for $C_{19}H_{20}FN_3O_2S$: C, 61.11; H, 5.40; N, 11.25; F, 5.09; S, 8.59. Found: C, 61.18; H, 5.44; N, 11.30; F, 4.97; S, 8.69.

**Competition Studies.** A solution of pyridine (8.1 mL, 100.0 mmol) in methylene chloride (40 mL) at 5 °C was treated with ethyl chloroformate (9.5 mL, 100.0 mmol). After 10 min, a methylene chloride (15 mL) solution containing a mixture of imidazo[2,1-*b*]thiazoles (5.0 mmol each) was added to the reaction. After 2 h, the reaction was quenched with water, and the product mixture was isolated by methylene chloride extraction. The molar concentration of products in this mixture was determined by

(12) Buu-Hoi, Ng. Ph.; Hoan, Ng.; Jacquignon, P.; Knoi, Ng. H. *J. Chem. Soc.* **1950**, 2766.

standard based HPLC. HPLC Conditions: Column and Water Associates μBondapak $C_{18}$ 10 μm, 3.9 mm ID × 30 cm; mobile phase, 650 mL of $CH_3OH$ (HPLC grade), 350 mL of $H_2O$ (HPLC grade), 1.2 g of $Na_2H_2PO_4$ (reagent grade); flow rate, 2.0 mL/min.

**Acknowledgment.** We wish to acknowledge our indebtedness to Edith Reich of the Analytical Chemistry department for elemental analyses and to the Mass Spectrometry Facility of the Physical and Structural Chemistry Department of Smith Kline and French Laboratories for spectral data.

# Studies on Lactams. 81. Enantiospecific Synthesis and Absolute Configuration of Substituted β-Lactams from D-Glyceraldehyde Acetonide†,[1]

Dilip R. Wagle, Chandra Garai, Julian Chiang, Michael G. Monteleone, Barbara E. Kurys, Timothy W. Strohmeyer, Vinod R. Hegde, Maghar S. Manhas, and Ajay K. Bose*

*Department of Chemistry and Chemical Engineering, Stevens Institute of Technology, Hoboken, New Jersey 07030*

*Received April 13, 1988*

Optically active 3,4-disubstituted 2-azetidinones have been prepared in good yield by the annelation of Schiff bases from D-glyceraldehyde acetonide with acid chlorides (or equivalent) and triethylamine. The utility of this enantiospecific synthesis was extended by the stereocontrolled modification of functional groups leading to optically active trans β-lactams. The absolute configuration of some key compounds was determined by chemical degradation. Modification of substituents on the β-lactam ring led to optically active intermediates for a variety of natural products, such as alkaloids, carbohydrates, and amino acids.

Stereocontrolled synthesis of β-lactams continues to be an area of intense activity.[2] The periodic discovery of new β-lactam antibiotics in nature sustains the interest of synthetic and medicinal chemists.[3] The potential of substituted 2-azetidinones for serving as efficient synthons for a variety of natural products has provided added interest.[4]

In the early stages of our studies[5] on β-lactams, we achieved a completely diastereoselective synthesis of a 6-epipenicillin V methyl ester (**4**) by using a chiral thiazoline (**2**) and an achiral acid chloride (**1**) as the reactants (Scheme I). The stereochemistry at the ring junction carbon (C-5) in **3** is determined by the configuration of the carboxyl group bearing carbon (C-3) since the carboxyl group is sterically less hindered in the exo position. The trans configuration of the β-lactam (resulting in the 6-epi configuration) appears to depend on the directive influence of the sulfur next to the ring junction. For reasons not clear, the presence of sulfur at either C-3 or C-4 induces trans stereochemistry in a 3,4-disubstituted 2-azetidinone.

Annelation of an acyclic imino compound led to β-lactam formation but with reduced diastereoselectivity. Thus, when an acyclic thioimidate, such as **5**[6] or **8**,[7] was used as the imino component, two isomeric β-lactams (**6** and **7** or **9** and **10**) were formed but both were trans β-lactams (Scheme II).

In the absence of a thio group in the acyclic imino component, again two β-lactams were formed, but both had the cis geometry (Scheme III). The diastereoselectivity varied depending on the nature of substituents on the amino compound from which the Schiff base was prepared. For instance, we[8] observed the formation of two cis β-lactams (**12a** and **13a**) in nearly 50:50 proportion by the reaction of an acid chloride (**1**) and triethylamine with a Schiff base (**11a**) from cinnamaldehyde and a D-threonine ester (Scheme III). Tenneson and Belleau[9] used a *tert*-butyldimethylsilyl ether of a D-threonine ester, e.g., **11b**, and achieved high diastereoselectivity (e.g., **12b** and **13b** were formed in 90:10 proportion) (Scheme III). This imino compound has two centers of asymmetry. The bulk of the substituents at the chiral center which is not adjacent to the imino group strongly affects the diastereoselectivity for β-lactam formation. When we[10,31] used the very bulky

† Dedicated to the memory of Professor James M. van der Veen.

(1) Studies on Lactams. 81. For Part 80, see: Wagle, D. R.; Garai, C.; Monteleone, M.; Bose, A. K. *Tetrahedron Lett.* **1988**, *29*, 1649.
(2) Labia, R.; Morin, C. *J. Antibiot.* **1984**, *37*, 1103.
(3) See, for example: Chevolot, L.; Chevolot, A. M.; Gajhede, M.; Larsen, C.; Anthoni, U.; Christophersen, C. *J. Am. Chem. Soc.* **1985**, *107*, 4542.
(4) (a) Manhas, M. S.; van der Veen, J. M.; Wagle, D. R.; Hegde, V. R.; Bari, S. S.; Kosarych, Z.; Ghosh, M.; Krishnan, L. *Indian J. Chem., Sect. B* **1986**, *25B*, 1095. (b) Hauser, F. M.; Rhee, R. P.; Ellenberger, S. R. *J. Org. Chem.* **1984**, *49*, 2236. (c) Wasserman, H. H.; Pearce, B. C. *Tetrahedron Lett.* **1985**, *26*, 2237 and references cited therein. (d) Crombie, L.; Jones, R. C. F.; Mat-Zin, A. R.; Osborne, S. *J. Chem. Soc., Chem. Commun.* **1983**, 960. (e) Crombie, L.; Jones, R. C. F.; Haigh, D. *Tetrahedron Lett.* **1986**, *27*, 5147. (f) Fliri, A.; Hohenlohe-Oehringen, D. *Chem. Ber.* **1980**, *13*, 607. (g) Fukuyama, T.; Frank, R. K.; Jewell, C. F. *J. Am. Chem. Soc.* **1980**, *102*, 2122. (h) Thomas, E. J.; Williams, A. C. *J. Chem. Soc., Chem. Commun.* **1987**, 992. (i) Baldwin, J. E.; Adlingtol, R. M.; Birch, D. J. *J. Chem. Soc., Chem. Commun.* **1985**, 256. (j) Ojima, I. *Asymmetric Reactions and Progress in Chemistry*; ACS Symposium Series; American Chemical Society: Washington, DC, 1982; No. 185, p 109. (k) Duhamel, P.; Goument, B.; Plaqeevent, J. C. *Tetrahedron Lett.* **1987**, *28*, 2595. (l) Kano, S.; Ebata, J.; Shibuya, S. *Heterocycles* **1980**, *14*, 43.
(5) Bose, A. K.; Spiegelman, G.; Manahs, M. S. *J. Am. Chem. Soc.* **1968**, *90*, 4506.
(6) Bachi, M. D.; Goldberg, O. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2332. See also: Bachi, M. D.; Breiman, R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 11.
(7) Kamiya, T. In *Recent Advances in the Chemistry of β-Lactam Antibiotics*; Elks, J., Ed.; spec. publ. no. 28, The Royal Society of Chemistry, June 1976, p 281.
(8) (a) Bose, A. K.; Anjaneyulu, B.; Bhattacharya, S. K.; Manhas, M. S. *Tetrahedron* **1967**, *23*, 4769. (b) Bose, A. K.; Manhas, M. S.; van der Veen, J. M.; Amin, S. G.; Fernandez, I. F.; Gala, K.; Gruska, R.; Kapur, J. C.; Khajavi, M. S.; Kreder, J.; Mukkavilli, L.; Ram, B.; Sugiura, M.; Vincent, J. E. *Tetrahedron* **1981**, *37*, 2321. (c) Vincent, J. E. Ph.D. Thesis, Stevens Institute of Technology, 1979.
(9) Tenneson, S. M.; Belleau, B. *Can. J. Chem.* **1980**, *58*, 1605.
(10) Hegde, V. R. Ph.D. Thesis, Stevens Institute of Technology, 1984.
(11) Hubschwerlen, C.; Schmidt, G. *Helv. Chim. Acta* **1983**, *66*, 2206. See also: Hubschwerlen, C.; Schmidt, G. European Patent 0073061, 1983.

0022-3263/88/1953-4227$01.50/0 © 1988 American Chemical Society