Antiinflammatory Activity of 5,6-Diaryl-2,3-dihydroimidazo[2,1-*b*]thiazoles. Isomeric 4-Pyridyl and 4-Substituted Phenyl Derivatives

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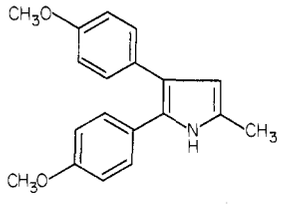
Isomeric 5(6)-(4-pyridyl)- and 6(5)-(4-substituted-phenyl)-2,3-dihydroimidazo[2,1-*b*]thiazoles were prepared by a mixed benzoin–imidazothione route, and their structures were assigned by spectral comparison to compounds of established substitution pattern. The structural assignment was confirmed by X-ray analysis. Examination of the compounds for antiinflammatory activity by an adjuvant arthritic rat assay revealed strikingly higher potencies for one analogous series than for their isomers. This selectivity was paralleled in the ability to stimulate cell-mediated immunity, as reflected in an oxazolone-induced contact sensitivity model. A drug–receptor complex is proposed that requires at least three sites of interactions.

Nonsteroidal antiinflammatory drugs (NSAID) are used in the treatment of a number of arthritic conditions, including rheumatoid arthritis.[1] Compounds that belong to this therapeutic group have diverse chemical structures with the common property of containing some easily ionized acidic functionality.[2] The discovery of nonacidic NSAID, i.e., bimetropyrol,[3] tiflamizole,[4] and BW-755C[5] (**1–3**) containing pyrrole, imidazole, and pyrazoline moie-



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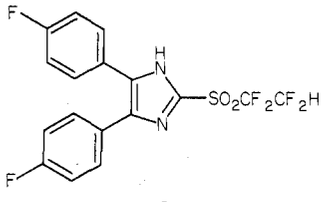

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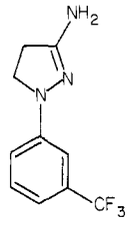

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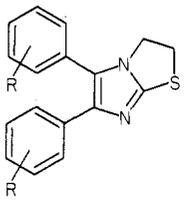

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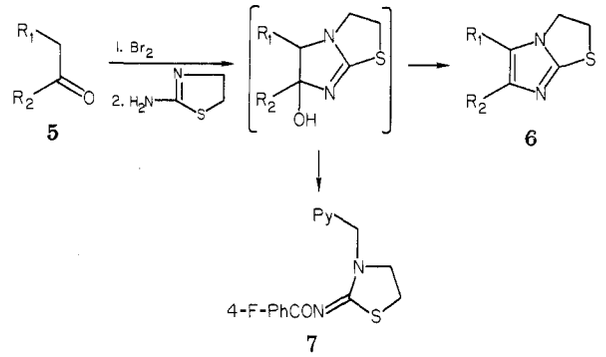
ties, respectively, appear to represent a second generation class with the potential of producing less gastric mucosal damage as a result of their lack of acidic properties. We have been interested in a subclass of these compounds, 5,6-diaryl-2,3-dihydroimidazo[2,1-*b*]thiazoles (**4**), which have the capacity to inhibit development of both the primary and secondary lesions in the adjuvant rat model of arthritis.[6] In addition, these compounds were found to accentuate the contact sensitivity response in the experimental model of low-grade contact sensitivity to oxazolone in mice.[7] This response is considered to reflect stimulation of suppressed cell-mediated immunity (CMI).

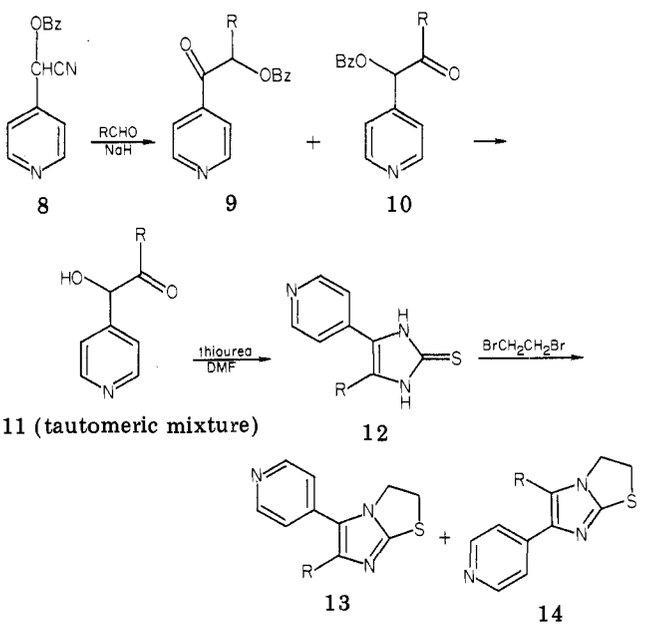
Structure–activity relationship (SAR) studies by us and others[8] revealed that the nature of the aryl substituents

Scheme I[a]



[a] a: R_1 = 4-CH_3OPh; R_2 = Ph. b: R_1 = Ph: R_2 = 4-CH_3OPh.

Scheme II[a]



[a] a: R = 4-CH_3OPh. b: R = 4-CH_3SPh. c: R = 4-FPh.

in **4** was critical for desirable biological activity. Strongly polar substituents, i.e., CH_3O, CH_3S, and F, in the para position of the phenyl rings, increased potency considerably.

The present study was undertaken to probe further into this substituent requirement along two clearly defined lines: to study the synthesis and biological properties of unsymmetrically 5,6-substituted imidazo[2,1-*b*]thiazolines

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(2) (a) Scherrer, R. A.; Whitehouse, M. W. *Med. Chem. (Academic)* **1974**, *13*, 29. (b) Lombardino, J. G.; Wiseman, E. H. *Trends Pharmacol. Sci.* **1981**, *2*, 132
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(7) (a) Griswold, D. E.; DiLorenzo, J. A.; Calabresi, P. *Cell Immunol.*, **1974**, *11*, 198. (b) Griswold, D. E.; Walz, D. T. *Inflammation* **1982**, *6*, 55.
(8) (a) Cherkofsky, S. C.; Sharpe, T. R. U.S. Patent 4 064 260, 1977. (b) Baetz, J. L. E. U.S. Patent 4 110 460, 1978.

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Table I. Adjuvant Arthritic Activity (Rat) and Cutaneous Oxazolone Induced Contact Sensitivity (Mouse) of 2,3-Dihydroimidazo[2,1-b]thiazoles

compd	adjuvant rat leg vol, % inhibn[a] injected leg day 3	injected leg day 16	uninjected leg: day 16	contact sensitivity, % stimulation[b] right hind paw
4 (R = 4-MeO)	−25[f]	−36[f]	−29[f]	+194[f] (variable[c])
4 (R Ph = 4-pyridyl)	+4, NS[g]	−7, NS[g]	+3, NS[g]	
13a	−15[d]	−20[d]	−21[d]	+59[d]
13b	−16[e]	−12, NS[g]	−16, NS[g]	+19[g]
13c	−27[f]	−38[f]	−44[f]	+69[f]
14a	0, NS[g]	−1, NS[g]	+37[f]	+42, NS[g]
14b	−7, NS[g]	−8, NS[g]	+18	+19, NS[g]
14c	+2, NS[g]	−4, NS[g]	+9, NS[g]	+15, NS[g]
prednisolone [20 mg/(kg day), po]	−28[f]	−42[f]	−54[f]	−12, NS[g]
levamisole (50 mg/kg)	0, NS[g]	+2, NS[g]	−1, NS[g]	+230[g]

[a] Tested at 50 mg/kg, po. [b] Tested at 25 mg/kg, po. [c] Active 1 out of 3 times tested. [d] $p = 0.05$, as judged by Student's t test. [e] $p = 0.01$, as judged by Student's t test. [f] $p = 0.001$, as judged by Student's t test. [g] NS = not significant; $p > 0.05$, as judged by Student's t test.

and to incorporate 4-pyridyl substituents into the series.

Chemistry. Unsymmetrically substituted imidazo[2,1-b]thiazoles (**6a,b**) were prepared regioselectively by condensation of appropriately substituted α-bromo ketones with 2-aminothiazoline, as illustrated in Scheme I. This method (A) of condensation is fully regiospecific, and the resulting position of the imidazole ring substituents is as indicated.

Attempted extension of this traditional route to the 4-pyridyl-substituted species via 4-pyridylmethyl 4-fluorophenyl ketone (**5**, R_1 = 4-pyridyl; R_2 = 4-FPh) led instead to **7** as the sole isolable product. A possible mechanistic explanation for this transformation invokes carbon–carbon bond cleavage at the tetrahedral intermediate stage as shown.

Our second approach required the intermediacy of hitherto unreported mixed pyridoins **11** as in Scheme II. Their synthesis was accomplished by a modification of a previously reported benzoin condensation.[9] 4-Pyridinecarboxaldehyde was converted to the benzoylated cyanohydrin **8**, which was condensed with various benzaldehydes in t-BuOH at ambient temperature.

Depending on the nature of the condensation catalyst and the duration of the reaction, the condensation with 4-methoxybenzaldehyde resulted in the isolation of the primary kinetic product **9a** or the thermodynamically more stable product **10a**. Both compounds **9a** and **10a** were found to be highly labile, and, under protic conditions, hydrolytic removal of the benzoyl group was impossible without concomitant cleavage of the central C–C bond. This nondiscriminant attack at the ketocarbonyl linkage was suppressed with bases sufficiently basic to effect enolization of the ketone, thereby decreasing the electrophilicity of that carbonyl, and which were also sufficiently nucleophilic to remove the benzoyl group. t-BuOK was most suitable for this process; after the addition of 2 equiv of t-BuOK to a mixture of **9a** and **10a**, a deep-burgundy solution resulted, whose workup after 30 min afforded a mixture of tautomeric α-hydroxy ketones **11a** in 50–70% yield. Carrying out a similar sequence of condensation and t-BuOK treatment provided analogous mixed pyridoins **11b** and **11c**. Further elaboration to the target imidazo[2,1-b]thiazoles **13** and **14** proceeded according to established procedures.[11,12] Treatment of **11** with thiourea furnished first imidazothiones **12**, which were subsequently cyclized with 1,2-dibromoethane. The final products were always obtained as 1:1 mixtures of isomers, easily separated by column chromatography or by HPLC methods. Structural identification of the isomers was based on ^{1}H NMR signal positions of the para substituents and phenyl protons. We observed in the proton NMR of compounds **6a** and **6b**, prepared by method A, that the para CH_3O and CH_3S substituents showed a clearly defined upfield shift in their signal when attached to the phenyl groups in the 6-position of the imidazole (Table II). For example, the difference in the CH_3O signal between the 6-(4-methoxyphenyl) and 5-(4-methoxyphenyl) compounds was 0.10 ppm (**6b** and **6a**, respectively). Similar differences in the ^{19}F NMR spectrum of **13c** vs. **14c** aided our structural assignment in this series. In the case of compound **13c**, structural assignment was confirmed by an X-ray analysis (Figure 1), which not only provided ultimate structural proof but also indicated that differences in the electronic environment of the substituents were due to coplanarity of the 6-phenyl group with the electron-deficient bridgehead nitrogen in the imidazole.

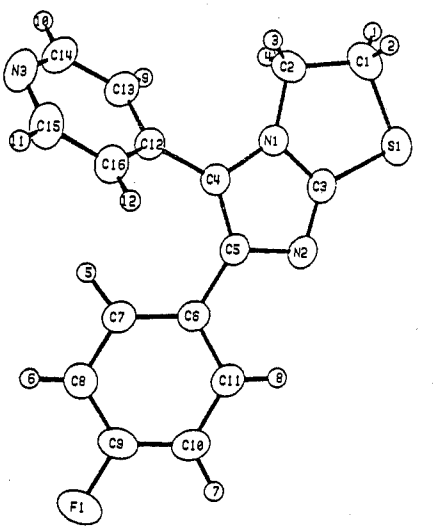

Figure 1. X-ray structure of **13c**.

Analytical and physical data for substituted imidazo[2,1-b]thiazoles are presented in Table II.

Biology. Antiinflammatory activity was determined by using an adjuvant arthritic rat assay system.[6] Test com-

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(10) Hamana, M.; Endo, T.; Saeki, S. *Tetrahedron Lett.* **1975**, 903.
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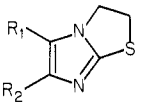
(12) Mazur, I. A.; Kochergin, P. H.; Fomenko, V. I. *Khim. Farm. Zh.* **1969**, *3*, 11.

Table II. Substituted Imidazo[2,1-*b*]thiazoles



compd	R_1	R_2	mp, °C	recrystn solvent	formula[a]	supportive ^{1}H NMR signals, δ: 4-substituent	supportive ^{1}H NMR signals, δ: phenyl
6a	4-CH_3O-Ph	Ph	228–231	2-PrOH	$C_{18}H_{16}N_2OS \cdot HBr$	3.64	6.70, 7.40
6b	Ph	4-CH_3O-Ph	273–274	2-PrOH	$C_{18}H_{16}N_2OS \cdot HBr$	3.72	6.80, 7.50
13a	Py	4-CH_3O-Ph	170–172	$CHCl_3$-Et_2O	$C_{17}H_{15}N_3OS$	3.67	6.60, 7.17
14a	4-CH_3O-Ph	Py	187–188	$CHCl_3$-Et_2O	$C_{17}H_{15}N_3OS$	3.88	7.00, 7.75
13b	Py	4-CH_3S-Ph	190–193	$CHCl_3$-Et_2O	$C_{17}H_{15}N_3S_2$	2.46	7.06, 7.40
14b	4-CH_3S-Ph	Py	210–213	$CHCl_3$-Et_2O	$C_{17}H_{15}N_3S_2$	2.55	7.23, 7.51
13c	Py	4-F-Ph	186–189	2-PrOH	$C_{16}H_{12}FN_3S$	39.4[b]	
14c	4-F-Ph	Py	165–167	2-PrOH	$C_{16}H_{12}FN_3S$	36.5[b]	

[a] All compounds were analyzed for C, H, and N, and analytical values were within ±0.4% of calculated values. [b] Upfield from TFAA internal standard.

pounds were administered daily, beginning on the day of the adjuvant injection and continued for 17 days, exclusive of days 4, 5, 11, and 12. Tests results were determined by comparing leg volumes of dosed animals with control arthritic vehicle groups. Immunoregulatory activity was evaluated by using low-grade contact sensitivity to oxazolone in C52B1/6 mice.[7] Compounds were administered on day 0, 30 min prior to sensitization to oxazolone, and the results were generated by comparing differences in leg volumes 24 h after challenge with oxazolone on the right hind paw. These are shown in Table I. For the purposes of comparison, we have also included the bis(methoxyphenyl) (**4**, R = 4-MeO) and dipyridyl (**4**, R-Ph = 4-pyridyl) compounds,[13] as well as levamisole and prednisolone.

The significantly higher degree of antiinflammatory activity and immunoregulatory activity found with the 5-(4-pyridyl)-6-aryl series of compounds **13** compared to the isomers **14** are apparent from Table I. We have no logical explanation at this time for the significant inflammatory activity of **14a** on day 16. Octanol/water partition coefficients of **13c** and **14c** were similar, 17.5 and 19.5. Thus, the differences in the degree of antiinflammatory activity does not appear to be a manifestation of different hydrophobicities. Support for this interpretation can be gained by considering compound **4** (R = 4-MeO), whose activity is quite comparable to **13a**, yet its partition coefficient, 2.5, is only one-fifth that of the pyridyl compounds. Based on our data, we speculate as a working hypothesis the existence of a drug–receptor complex requiring at least three sites of attachment, wherein the 5-substituent and the electron-rich nitrogen of the imidazole provide hydrogen-bonding sites and the 6-aryl substituent interacts with lipophilic residues. Lipophilic binding is enhanced by substituents of decreasing size in the para position of the phenyl groups.

Experimental Section

Melting points were obtained in a Thomas-Hoover Uni-melt apparatus and are uncorrected. NMR spectra were recorded on a Hitachi Perkin-Elmer R-24 spectrometer, and spectral positions are listed in units downfield from Me_4Si. Elemental analyses are denoted by symbols of the elements and are within ±0.4% of calculated values.

1-Phenyl-2-(4-methoxyphenyl)ethanone (5a). To a suspension of $AlCl_3$ (500 g) in 500 mL of benzene was slowly added a solution of 4-methoxyphenylacetyl chloride (35.3 g, 0.19 mol) in CH_2Cl_2 (200 mL) with external cooling. The reaction was stirred overnight at ambient temperature, and the excess $AlCl_3$ was carefully decomposed by the addition of H_2O (100 mL). After the organic layer was separated from the aqueous layer, the solvent was removed at reduced pressure, and the residual oil was distilled at 150–165 °C (2–5 mmHg). The distillate was further purified by chromatography (EtOAc/cyclohexane, SiO_2) to obtain 5.22 g of **5a**.[14]

5-(4-Methoxyphenyl)-6-phenyl-2,3-dihydroimidazo[2,1-*b*]thiazole (6a). Method A. A solution of **5a** (5.22 g, 23 mmol) and bromine (3.36 g) in CCl_4 (125 mL) was irradiated with a 250-W GE sunlamp until the evolution of HBr was no longer detected. After removal of the solvent at reduced pressure, the residue was taken up in $CHCl_3$ (200 mL), washed with 5% Na_2CO_3, and dried over anhydrous $MgSO_4$. The solution was filtered, and the filtrate was evaporated under reduced pressure to yield an oil, which solidified after trituration with Et_2O to obtain 4.5 g (65%) of a solid, which was used in the next step without purification.

The α-bromo ketone (9.0 g, 29.5 mmol) and 2-aminothiazoline (6.0 g, 59.1 mmol) were dissolved in acetonitrile (100 mL) at room temperature, and a few grams of molecular sieves (3Å) was added. After stirring overnight at ambient temperature, the mixture was filtered to remove the powdered molecular sieves. The filtrate was condensed at reduced pressure, and the glassy solid was chromatographed on SiO_2 using EtOAc–cyclohexane (1:4), yielding 6.0 g (66%) of **6a**, which was purified as the HBr salt.

1-(4-Methoxyphenyl)-2-phenylethanone (5b). Benzyl 4-hydroxyphenyl ketone (Aldrich Chemical Co.; 5.0 g, 23.5 mmol) was dissolved in 5 N Na_2CO_3 (50 mL), and dimethyl sulfate (10.0 mL) was added dropwise. The pH of the solution was maintained at 9.5 by the addition of solid Na_2CO_3. The precipitated product was filtered and recrystallized from MeOH.[15]

5-Phenyl-6-(4-methoxyphenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (6b). The preparation of the α-bromo ketone and its condensation with 2-aminothiazoline followed the procedure described for **5a**. The yield of the final product was 24%, purified as the HBr salt.

2-[(4-Fluorobenzoyl)imino]-3-(4-pyridylmethyl)thiazoline (7). A solution of 4-fluorophenyl 4-pyridylmethyl ketone[16] (5.0 g, 22 mmol) in 100 mL of CH_2Cl_2 was treated with an equimolar quantity of bromine in 10 mL of CH_2Cl_2. Immediate discharge of the coloration was observed. 2-Aminothiazoline (6.75 g, 66 mmol) was added to the colorless solution, which was stirred overnight at room temperature, under N_2. The reaction mixture was diluted with 100 mL of CH_2Cl_2 and washed with 5% sodium carbonate solution (3 × 25 mL), water, and brine; after drying over $MgSO_4$, the solution was evaporated. Dry column chromatography on silica gel with ethyl acetate and ether eluant (1:1) resulted in 0.9 g (13%) of crystalline product, mp 118.5–9.5 °C. Anal. ($C_{16}H_{14}FN_3OS$) C, H, N.

1-(Benzoyloxy)-1-(4-pyridyl)acetonitrile (8). To an aqueous phase containing sodium cyanide (19.6 g, 0.4 mol) and benzyl-

(13) A paper describing these compounds is in preparation.

(14) Jenkins, S. S. *J. Am. Chem. Soc.* **1932**, *54*, 1155.
(15) Hill, P.; Short, W. F. *J. Am. Chem. Soc.* **1935**, *57*, 1123.
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trimethylammonium chloride (3.0 g, 13 mmol) in 75 mL of water was added 4-pyridinecarboxaldehyde (10 g, 0.10 mol) in 100 mL of CH_2Cl_2 at 0.5 °C. The mixture was stirred vigorously with a magnetic stirrer. After 10 min of equilibration, benzoyl chloride (14.0 g, 0.10 mol) in 50 mL of CH_2Cl_2 was added over a period of 30 min. Stirring was discontinued, and the two phases were separated. The organic phase was washed with 5% sodium carbonate (3 × 30 mL), water, and brine and then dried over $MgSO_4$. The solution was filtered, and the filtrate was evaporated to an oil. The oily residue was extracted by gently heating with ether (10 × 50 mL) on the steam bath, and the combined ethereal extracts were concentrated under reduced pressure to 80 mL. Crystallization, after cooling, yielded 8.0 g (40%) of the desired product, mp 80–82 °C. Anal. ($C_{14}H_{10}N_2O_2$) C, H, N.

1-(4-Pyridyl)-2-(4-methoxyphenyl)-2-(benzoyloxy)-ethanone (9a) and 1-(4-Methoxyphenyl)-2-(benzoyloxy)-2-(4-pyridyl)ethanone (10a). A solution of **8** (5.0 g 21 mmol) and arylcarboxaldehyde (21 mmol) in 50 mL of *tert*-butyl alcohol was stirred with NaH (1.0 g, 50% oil, 21 mmol) at ambient temperature for 20 min until TLC (silica gel, ether) indicated the disappearance of starting materials and formation of a single product. Stirring for an additional 35–40 min resulted in the partial transformation of the intermediate product into a second, slower moving material on TLC. The reaction was quenched after 50 min in ice–water and was extracted with chloroform. After being dried, the chloroform extract was evaporated to an oil, which was chromatographed on silica gel with ether. The faster moving compound (**9**; R_f 0.4) was obtained in 0.7-g yield: mp 117–118 °C; IR ν_{max} 1709, 1686, 1605, 1258, 1111, 840 cm^{-1}; ^1H NMR δ 8.7 (d, J = 6 Hz, 2 H), 8.10 (q, J = 2.5 and 8 Hz, 2 H), 7.65 (d, J = 6 Hz, 2 H), 7.40 (m, 5 H), 6.95 (s, 1 H), 6.90 (d, J = 7 Hz, 2 H), 3.70 (s, 3 H). Anal. ($C_{21}H_{17}NO_4 \cdot {}^1/_8H_2O$) C, H, N.

The slower moving compound (**10**; R_f 0.25) was obtained in 3.05-g yield: mp 116–118 °C; IR ν_{max} 1695, 1667, 1587, 1250, 1176, 1111, 719; ^1H NMR δ 8.73 (d, J = 6 Hz, 2 H), 8.08 (q, J = 6 and 8 Hz, 4 H), 7.46 (m, 5 H), 7.05 (s, 1 H), 6.96 (d, J = 8 Hz, 2 H), 3.83 (s, 3 H). Anal. ($C_{21}H_{17}NO_4$) C, H, N.

1-Aryl-2-hydroxy-2-(4-pyridyl)ethanones (11). The above procedure for the benzoyl compounds was followed with the modification of adding an oil suspension of KH (42 mmol) after the first phase of the reaction was complete (1.5 h). A deep-burgundy colored solution was obtained immediately, whose TLC indicated a single compound after 1.5 h. The solution was quenched in a 100 mL of ice–water and thoroughly extracted with chloroform (4 × 50 mL). After washing and drying, the organic extract was concentrated to an oil at reduced pressure, which crystallized upon trituration with Et_2O.

The 1-(4-methoxyphenyl) compound (11a; 2.6 g) was obtained in 50% yield, mp 135–137 °C. Anal. ($C_{14}H_{13}NO_2H_2O$) C, H, N.

The 1-[(4-methylthio)phenyl] compound **11b** (3.2 g) was obtained in 65% yield, mp 127–180 °C. Anal. ($C_{14}H_{13}NO_2S \cdot 0.25H_2O$) C, H, N.

The 1-(4-fluorophenyl) compound **11c** was used directly in the next step.

4-Aryl-5-(4-pyridyl)imidazole-2-thiones (12). Thiourea (5.3 g, 70 mmol) was added to a solution of **11** (37 mmol) in dimethylformamide (140 mL), and the mixture was refluxed for 4 h. The solvent was concentrated to one-half of the original volume and cooled overnight at 0 °C. The crystalline material was filtered, washed with water, and dried overnight at 70 °C (0.02 mmHg).

The 4-(4-methoxyphenyl)-5-(4-pyridyl) compound **12a** was formed in 68% yield, mp 280 °C. Anal. ($C_{15}H_{13}N_3OS$) C, H, N.

The 4-[4-(methylthio)phenyl]-5-(4-pyridyl) compound **12b** was formed in 65% yield, mp 350 °C. Anal. ($C_{15}H_{13}N_3S_2$) C, H, N.

The 4-(4-fluorophenyl)-5-(4-pyridyl) compound **12c** was formed in 40% yield based on the benzoylcyanohydrin condensation, mp 386–388 °C. Anal. ($C_{14}H_{10}FN_3S$) C, H, N.

Isomeric 6-Aryl-5-(4-pyridyl)- and 5-Aryl-6-(4-pyridyl)-2,3-dihydroimidazo[2,1-*b*]thiazoles (13 and 14). Compounds **12** (12.5 mmol) were suspended in dimethylformamide (100 mL), and sodium hydride (0.62 g of 40% oil, 13.0 mmol) was added. Salt formation was allowed to proceed at ambient temperature for 0.5 h, 1,2-dibromoethane (2.29 g, 16.0 mmol) was added, and the solution was stirred overnight. Solid anhydrous potassium carbonate (2.8 g, 20 mmol) was added to this solution, and the reaction mixture was refluxed for 1.5 h. Dilution of the solution with 200 mL of ice–water precipitated the products. The crude product mixtures were separated by "flash column chromatography"[17] with 2-PrOH–ether (1:2). Physical properties and supportive NMR signals are shown in Table II.

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Registry No. **5a**, 24845-40-7; **5a** (α-bromo ketone), 56913-16-7; **5b**, 1023-17-2; **5b** (α-bromo ketone), 1889-77-6; **6a**, 64997-34-8; **6b**, 87532-36-3; **7**, 87532-35-2; **8**, 72873-67-7; **9a**, 87532-37-4; **10a**, 87532-38-5; **11a**, 87532-39-6; **11b**, 87532-40-9; **11c**, 87532-41-0; **12a**, 72882-73-6; **12b**, 72882-74-7; **12c**, 72882-75-8; **13a**, 72873-70-2; **13b**, 72873-72-4; **13c**, 72873-74-6; **14a**, 72873-71-3; **14b**, 72873-73-5; **14c**, 72873-75-7; benzene, 71-43-2; 4-methoxyphenylacetyl chloride, 4693-91-8; 2-aminothiazoline, 1779-81-3; benzyl 4-hydroxyphenyl ketone, 2491-32-9; 4-fluorophenyl 4-pyridylmethyl ketone, 6576-05-2; sodium cyanide, 143-33-9; benzyltrimethylammonium chloride, 56-93-9; 4-pyridinecarboxaldehyde, 872-85-5; 1,2-dibromoethane, 106-93-4; thiourea, 62-56-6.

(17) Still, W. C. *J. Org. Chem.* **1978**, 2933.