Heteroarylation of 6-Aryl-2,3-dihydroimidazo[2,1-*b*]thiazole with *N*-(Ethoxycarbonyl)heteroaromatic Salts [1]

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Received October 10, 1989
Revised May 28, 1993

The ethyl chloroformate salts of a variety of benzo-fused six membered π-deficient heteroaromatics, including quinoline, isoquinoline, 4-chloroquinoline, 3-bromoquinoline, phthalazine, and quinazoline, reacted with 6-aryl-2,3-dihydroimidazo[2,1-*b*]thiazole at the 5-position. The dihydroheteroaromatic adducts were oxidized by *o*-chloranil, sulfur, or electrochemical methodology to form the 5-heteroaromatic-6-aryl-2,3-dihydroimidazo[2,1-*b*]thiazoles, **10-15**. In each example, the regiochemistry of addition to the heteroaromatic ring was established.

J. Heterocyclic Chem., **30**, 1663 (1993).

In previous communications [2,3], we described new approaches for the formation of 5-(4-pyridyl)-6-aryl-2,3-dihydroimidazo[2,1-*b*]thiazoles. This class of compounds was of interest as potential non-steroidal antiinflamatory agents for the treatment of a number of arthritic conditions [4]. The syntheses we developed involved the introduction of an *N*-(ethoxycarbonyl)pyridinium salt into the 5-position of a 6-arylimidazo[2,1-*b*]thiazoline substrate, followed by oxidation of the intermediate 1,4-dihydropyridyl adduct to the desired compound. A wide range of 6-aryl-2,3-dihydroimidazo[2,1-*b*]thiazoles, containing both electron withdrawing and electron donating groups on the phenyl ring readily underwent addition to the pyridine-ethyl chloroformate salt. A number of reagents successfully oxidized the *N*-(ethoxycarbonyl)-1,4-dihydropyridine group, including sulfur, potassium *tert*-butoxide/air, benzoquinone, and ceric ammonium nitrate. The reaction mechanism that was proposed invoked the formation of an electrophilic pyridinium salt which reacted with the highly nucleophilic imidazo[2,1-*b*]thiazoline moiety to form the adduct.

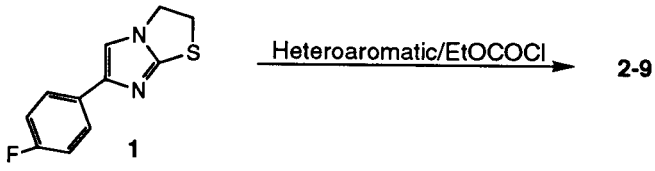
To extend the scope of this methodology, we explored the range of other electrophilic species that could successfully undergo this reaction. Heteroarylation by the attack of a *N*-acyl heteroaromatic cation on a nucleophilic substrate has been well documented [5]. The *N*-acyl salts of a variety of pyridine bases such as quinoline, isoquinoline, and acridine have reacted with many types of heterocyclic nucleophiles, including indoles [6], pyrroles [7], and furans [8], as well as activated aromatic rings such as anilines [9]. It seemed possible to apply this methodology to the 6-aryl-2,3-dihydroimidazo[2,1-*b*]thiazole system, using the corresponding *N*-alkoxycarbonyl moieties. Because of its ready availability and our previous familiarity with its reactivity in the pyridination reaction, we employed 6-(4-fluorophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole, **1**, as the nucleophilic substrate in this series of reactions. However, these heteroarylation reactions are not specific for this compound as 6-phenyl-2,3-dihydroimidazo[2,1-*b*]thiazole and other 6-aryl analogs reproduced the results obtained for **1** [10]. The experimental procedure that was used closely followed our best conditions for the pyridination reaction.

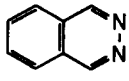
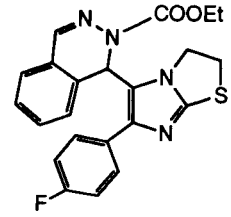
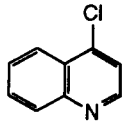
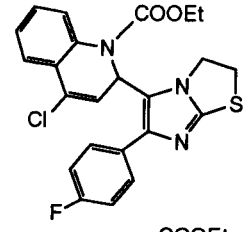
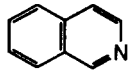
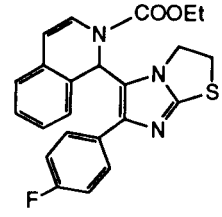
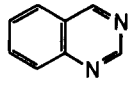
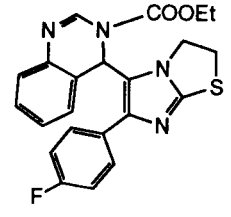
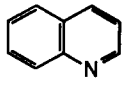
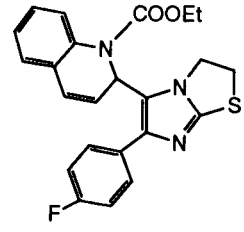
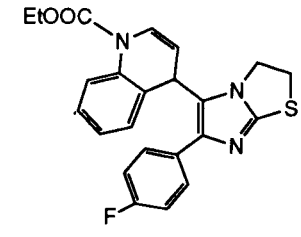
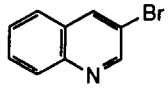
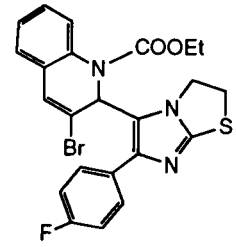
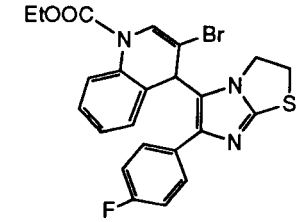
The following heteroaromatics were successfully substituted for pyridine in the heteroadduct formation: quinoline, isoquinoline, 4-chloroquinoline, 3-bromoquinoline, phthalazine, and quinazoline. In general, the ethyl chloroformate salts of these benzo-fused six-membered π-deficient heteroaromatics were more reactive than the corresponding pyridinium salt in reaction with **1**, since a smaller excess of the salt was required to complete the reaction. Several heterocycles gave no product formation in this reaction and resulted in the recovery of both starting materials. These included 2-chloroquinoline, 2-chloropyridine, 4-chloropyridine, acridine, and phenanthridine. Addition of the ethyl chloroformate salts of lepidine, quinaldine, and quinoxaline resulted in the decomposition of both the heteroaromatic moiety and **1**, without any discernable product formation. The results obtained for 2- and 4-methylquinoline were in agreement with literature precedent which demonstrated the instability of the *N*-acyl salts of these compounds and their tendency to dimerize [11]. The failure of the quinoxaline adduct to successfully add to **1** was in contrast to the reported reaction of *N*-acylquinoxalinyl salts with indoles [12], and may be due to the inherent instability of the resulting addition product.

Table I lists the results of a series of heteroarylation reactions on the substrate **1**. Phthalazine readily reacted with **1** to form the dihydrophthalazinyl adduct **2**. 4-Chloroquinoline-ethyl chloroformate reacted with **1** to

Table I

Heteroarylation of 6-(4-Fluorophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole, **1**



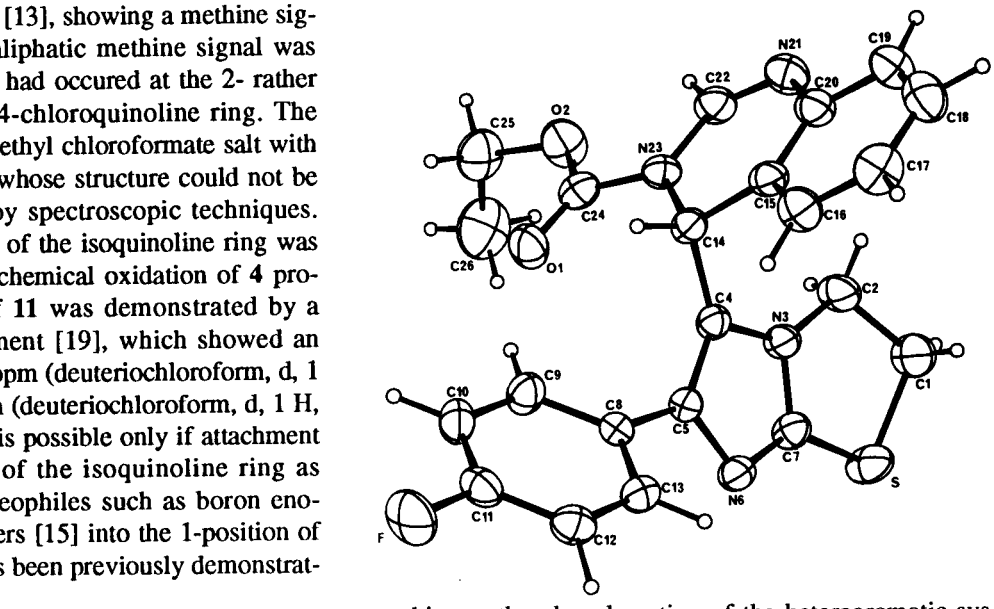
heteroaromatic	product	
		**2**
		**3**
		**4**
		**5**
		**6**
		**7**
		**8**
		**9**

form adduct **3**. Its structure was assigned by a ^{13}C-INEPT nmr experiment [13], showing a methine signal at 49.1 ppm. Such an aliphatic methine signal was possible only if substitution had occured at the 2- rather than the 4-position of the 4-chloroquinoline ring. The reaction of the isoquinoline-ethyl chloroformate salt with **1** gave a single product, **4**, whose structure could not be unambiguously identified by spectroscopic techniques. Addition into the 1-position of the isoquinoline ring was established after the electrochemical oxidation of **4** produced **11**. The structure of **11** was demonstrated by a ^{1}H-^{1}H COSY nmr experiment [19], which showed an isolated AB system at 8.67 ppm (deuteriochloroform, d, 1 H, J = 5.5 Hz) and 7.93 ppm (deuteriochloroform, d, 1 H, J = 5.5 Hz). Such a system is possible only if attachment occured at the 1-position of the isoquinoline ring as expected. Addition of nucleophiles such as boron enolates [14] and silyl enol ethers [15] into the 1-position of the isoquinolinyl reagent has been previously demonstrated.

The *N*-(ethoxycarbonyl)quinazolinyl salt presented both the 2- and the 4-position as possible ring sites for addition to **1**. Hplc and tlc demonstrated that only one product, **5**, was formed in the reaction. An X-ray crystal structure established the identity of the product as 5-(1-carboethoxy-1,4-dihydro-4-quinazolinyl)-6-(4-fluorophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (Figure 1) in which addition had occured across the highly localized 3,4 double bond. This result was in agreement with previous literature reports in which quinazoline reacted with nucleophiles [16], including Grignard reagents [17] at the 4-position of the heteroaromatic ring.

Quinoline added readily to the imidazo[2,1-*b*]thiazoline substrate **1**. In contrast to pyridine, this reaction was not regioselective, and gave a mixture of products resulting from addition to both the 2- and the 4-positions of the quinoline ring. The regioisomers were inseparable by normal phase chromatographic methods. Hplc showed a mixture of products (*ca.* 1:1) which could be separated by reverse phase column chromatography. In additon, recrystallization of the product mixture afforded the more crystalline adduct **6** as a pure material and a mother liquor enriched in isomer **7**. The early eluter, **6**, showed the methine group at 48.5 ppm (^{13}C, deuteriochloroform) and 6.51 ppm (^{1}H, deuteriochloroform, dd, 1 H, ^{3}J = 5.9 Hz, ^{4}J = 1.7 Hz) in the ^{13}C-^{1}H COSY nmr spectrum [18]. ^{1}H-^{1}H COSY spectrum [19] demonstrated that the methine proton was coupled to the vinyl protons at the 3-position (5.97 ppm, dd, J = 5.9 Hz, J = 9.5 Hz) and the 4-position (6.58 ppm, d, J = 9.5 Hz) of the heterocyclic ring. The 4-proton signal was broadened due to coupling to the phenyl protons and therefore the small coupling to the methine was not resolved. No connectivity of the

Figure 1. X-ray crystallographic structure of **5**.



methine to the phenyl portion of the heteroaromatic system was observed, confirming substitution of the imidazothiazole ring at the 2-position of the quinoline ring. In contrast, the relevant methine of the late eluter, **7**, was observed at 32.8 ppm (^{13}C, deuteriochloroform) and 5.20 ppm (^{1}H, deuteriochloroform, m, 1 H). This was coupled to the vinyl protons at the 2-position (7.23 ppm, dd, J = 2.1 Hz, J = 7.5 Hz) and the 3-position (5.23 ppm, dd, J = 3.2 Hz, J = 7.5 Hz) and the the ortho phenyl proton at the 5-position of the heteroaromatic ring (7.00 ppm, d, J = 7.6 Hz). This latter fact confirmed that attachment occured at the the 4-position of the quinoline ring. 3-Bromoquinoline gave a similar mixture of isomeric products (*ca.* 1:1), **8** and **9**.

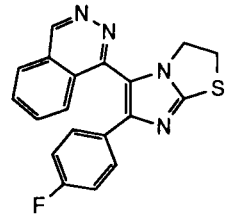
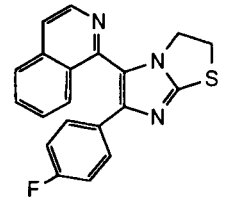
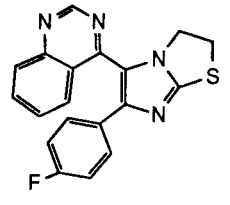
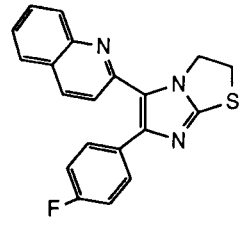
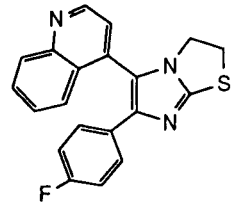
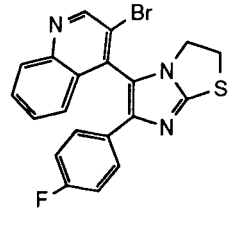
The heterocyclic adducts **2-9** were not as readily oxidized as the pyridine analog. Methodology that had been previously successful either failed to give any reaction (benzoquinone, chromium trioxide) or caused decomposition (potassium *tert*-butoxide/air). The use of *o*-chloranil in refluxing toluene [20] successfully oxidized most compounds in yields ranging from mediocre to good (35-75%). In isolated cases, either electrochemical methodology or sulfur [21] in refluxing mesitylene effected oxidation. Table II lists the results of the oxidation of **2-9**.

The phthalazinyl adduct **2** and the quinazolinyl adduct **5** were both oxidized with *o*-chloranil to give **10** and **12**, respectively. The structure of **12** confirmed that addition had occured at the 4-position of the quinazoline ring. No method was found for the efficient oxidation of the 4-chloroquinolinyl adduct **3**. Chromium trioxide did not react with **3** while other reagents, including *o*-chloranil, caused decomposition without any discernable product formation.

Electrochemical oxidation of **4** cleanly produced a single product, **11**, which was identified as 5-(1-isoquinolinyl)-6-(4-fluorophenyl)-2,3-dihydroimidazo[2,1-*b*]-thiazole. The cyclic voltammogram of **4** in 0.1 *M* hydrochloric acid:acetonitrile, using either a platinum wire or a glassy carbon working electrode, indicated an irreversible oxidation peak at +1.5 V vs saturated calomel electrode, possibly due to the oxidation of the dihydroiso-

Table II

Oxidation of *N*-Ethoxycarbonylheteroaromatic Imidazothiazoles, **2-9**

compound	product		method
2		**10**	*o*-chloranil
4		**11**	electrochemistry
5		**12**	*o*-chloranil
6+7		**13**	*o*-chloranil
6+7		**14**	sulfur
8+9		**15**	*o*-chloranil

quinoline moiety to isoquinoline. A controlled-potential electrolysis of **4** under these condtions gave a 57% yield of **11**. In cases **2**, **3**, **5-9**, this same methodology produced a complex mixture of products which included the corresponding sulfoxide, sulfone, and **1**.

Oxidation of the quinoline product mixture of **6** and **7** gave surprising results. Employing *o*-chloranil as the oxidant, only 5-(2-quinolinyl)-6-(4-fluorophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole **13** was isolated; the 4-quinolinyl adduct **7** apparently decomposed under the reaction conditions. Conversely, sulfur oxidation in refluxing mesitylene provided a mixture of 5-(4-quinolinyl)-6-(4-fluorophenyl)-2,3-dihydroimidazo [2,1-*b*]thiazole **14** and unreacted 2-quinolinyl adduct **6**, which were readily separated by normal phase silica chromatography. When the pure adduct **6**, isolated by column chromatography, was oxidized with *o*-chloranil, **13** was the sole product. Sulfur oxidation of pure **7**, isolated by reverse phase column chromatography, produced **14**. Thus we were able to definitively establish the structure of compounds **6** and **7** through the assignments given to **13** and **14**. These results confirmed the identification given by ^{1}H-^{1}H COSY nmr experiments.

In the case of the 3-bromoquinolinyl adducts **8** and **9**, the mixture was not separated, but treated with *o*-chloranil. However, in this example, 5-(4-(3-bromoquinolinyl))-6-(4-fluorophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole **15** was formed, while a single isomer of the starting material was recovered from the reaction mixture. Identical results were obtained when sulfur in refluxing mesitylene was employed as the oxidant. The methine group of the unoxidized compound was observed at 54.5 ppm (^{13}C, deuteriochloroform) and 6.55 ppm (^{1}H, deuteriochloroform, d, 1 H, ^{4}J = 0.8 Hz) in the ^{13}C-^{1}H COSY nmr spectrum [18] (Figure 2). This was coupled to the vinyl proton at the 4-position (6.88 ppm, ^{4}J = 0.8 Hz) of the quinoline ring, while no coupling to the phenyl protons of the quinoline ring was observed in the ^{1}H-^{1}H COSY nmr spectrum [19] (Figure 3). This data was consistent with the attachment of the imidazo[2,1-*b*]thiazoline substrate at the 2-position of the 3-bromoquinoline ring. Thus 5-((1-ethoxycarbonyl)-1,2-dihydro-3-bromo-2-quinolinyl)-6-(4-fluorophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole, **8**, was recovered from the *o*-chloranil oxidation. Oxidation of the dihydroheteroaromatic adducts seemed to depend strongly on the nature of the individual substrate, and a single methodology was not sufficient for this entire class of compounds.

In conclusion, we have demonstrated that a number of benzo-fused six-membered π-deficient heteraromatics

Figure 2. ^{13}C-^{1}H COSY spectrum of **8**.

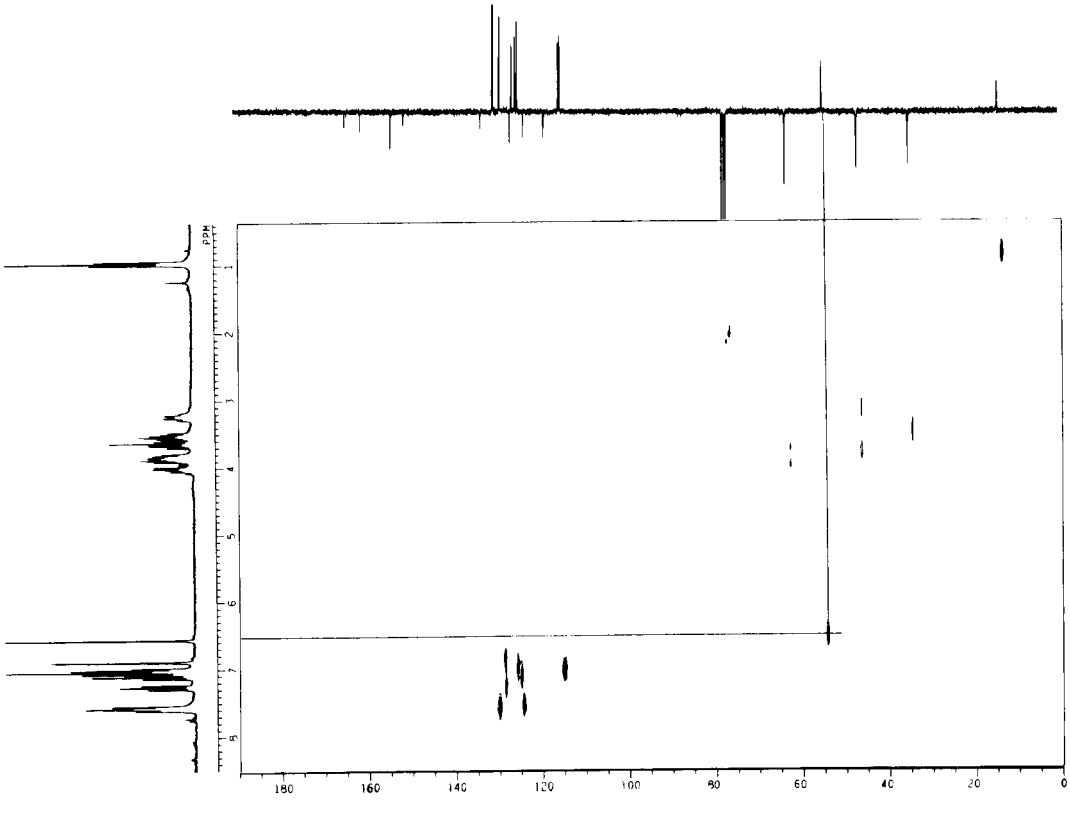
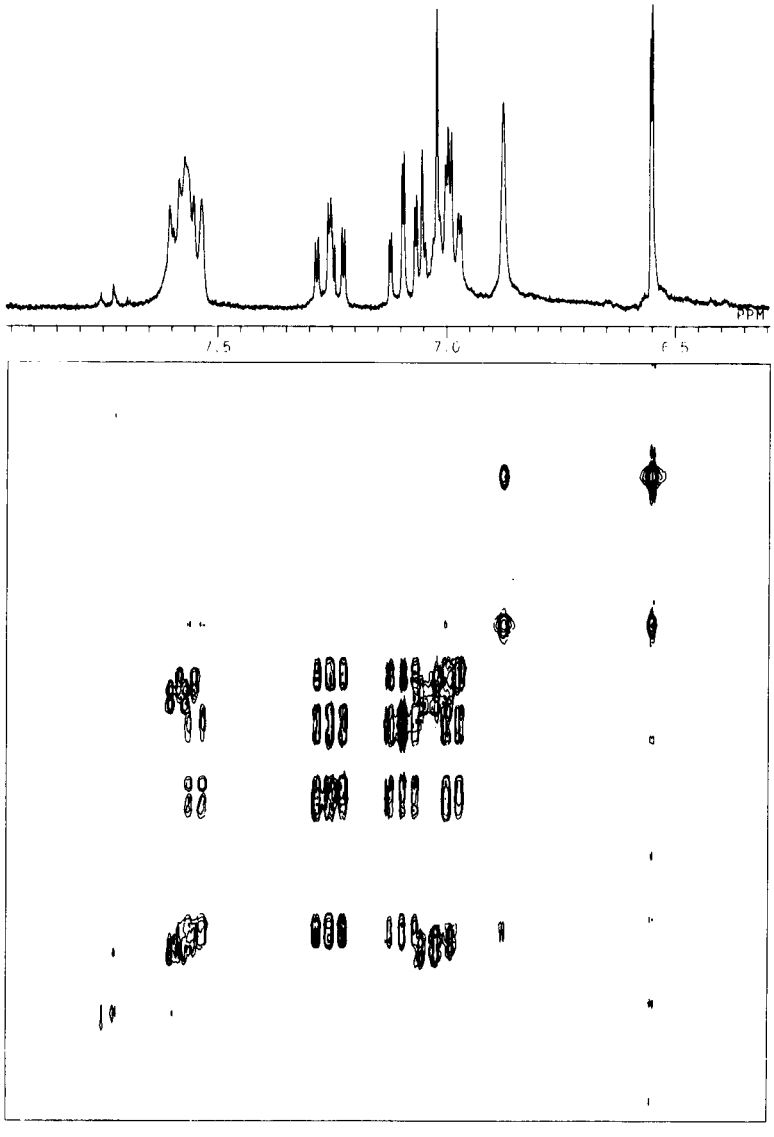


Figure 3. ^{1}H-^{1}H spectrum of 8.



can form an ethyl chloroformate salt capable of electrophilic attack on the 5-position of 6-(4-fluorophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole in a manner similar to pyridine. These compounds can then be oxidized to a unique class of 5-heteroaromatic-6-aryl-2,3-dihydroimidazo[2,1-*b*]thiazoles.

EXPERIMENTAL

Melting points were measured on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Ir spectra were recorded on a Perkin-Elmer model 283 spectrophotometer. Single sweep proton nmr spectra were recorded on a Varian EM360L spectrometer. Fourier transform ^{13}C and ^{1}H spectra were obtained on a JEOL GX 270 NMR spectrometer at 67.8 and 270.05 MHz respectively. The system was equipped with a 5 mm $^{1}H/^{13}C$ dual probe and a DEC RSX11M operating system. Proton chemical shifts are reported in ppm from tetramethylsilane. The center peak of the solvent multiplet at 77.0 ppm served as a reference for the ^{13}C spectra.

6-(4-Fluorophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole **1** was synthesized by the condensation of 2-aminothiazoline and 2-chloro-4'-fluoroacetophenone according to the procedure previously reported [3].

General Procedure for the Preparation of 5-*N*-(Ethoxycarbonyldihydroheteroaromatic)-6-(4-fluorophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazoles **2-9**.

A solution of **1** (2.97 g, 13.5 mmoles) and the corresponding heteroaromatic compound (38.4 mmoles) in methylene chloride (20 ml) was cooled to 0-5°. Ethyl chloroformate (3.7 ml, 38.7 mmoles) was added (15-20 minutes) so that the reaction temperature did not exceed 10°. The reaction was allowed to warm to ambient temperature overnight, and was then quenched with

water. The organic solution was treated with brine, and dried (anhydrous magnesium sulfate). The organic solvents were removed *in vacuo*, and the residue was purified by column chromatography on silica gel with diethyl ether-petroleum ether (3:1) as an eluant to give **2-9**.

5-((2-Ethoxycarbonyl)-1,2-dihydro-1-phthalazinyl)-6-(4-fluorophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (**2**).

Compound **2** was obtained in 62% yield after recrystallization from ethyl acetate-hexane, mp 93.5-95°; ^{1}H nmr (deuteriochloroform): δ 1.27 (t, 3 H, J = 7.0 Hz, CH_3), 3.43-4.23 (m, 6 H, CH_2CH_2, OCH_2), 6.67-7.95 (m, 10 H, Ar, CH); ir (potassium bromide): 2980, 1680, 1470, 1310, 1130, 850, 760 cm^{-1}.

Anal. Calcd. for $C_{22}H_{19}FN_4O_2S$: C, 62.55; H, 4.53; N, 13.26; S, 7.59. Found: C, 62.61; H, 4.86; N, 12.71; S, 7.42.

5-((1-Ethoxycarbonyl)-1,2-dihydro-4-chloro-2-quinolinyl)-6-(4-fluorophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (**3**).

Compound **3** was obtained in 42% yield after recrystallization from ethyl acetate-hexane, mp 187-188°; ^{1}H nmr (deuteriochloroform): δ 0.98 (t, 3 H, J = 7.0 Hz, CH_3), 3.13-4.28 (m, 6 H, CH_2CH_2, OCH_2), 6.10 (d, 1 H, J = 6.5 Hz, CH), 6.52 (d, 1 H, J = 6.5 Hz, Cl=CH), 6.78-7.70 (m, 8 H, Ar); ir (potassium bromide): 2980, 1715, 1480, 1280, 1220, 840, 750 cm^{-1}.

Anal. Calcd. for $C_{23}H_{19}ClFN_3O_2S$: C, 60.59; H, 4.20; N, 9.22. Found: C, 60.53; H, 4.38; N, 9.47.

5-((2-Ethoxycarbonyl)-1,2-dihydro-1-isoquinolinyl)-6-(4-fluorophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (**4**).

Compound **4** was obtained in 75% yield after recrystallization from ethanol, mp 183-184°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.04 (t, 3 H, J = 7.0 Hz, CH_3), 3.66-4.22 (m, 6 H, CH_2CH_2, OCH_2), 5.85 (d, 1 H, J = 8.0 Hz, CH-N), 6.88-7.22 (m, 8 H, Ar), 7.74-7.80 (m, 2 H, CH=CH); ir (film): 1700, 1630, 1500, 1400, 1370, 1320, 1220, 1160, 1120, 1095, 920, 830 cm^{-1}.

Anal. Calcd. for $C_{23}H_{20}FN_3O_2S$: C, 65.54; H, 4.78; N, 9.97. Found: C, 65.50; H, 4.87; N, 9.95.

5-((3-Ethoxycarbonyl)-3,4-dihydro-4-quinazolinyl)-6-(4-fluorophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (**5**).

Compound **5** was obtained in 54% yield after recrystallization from ethyl acetate-hexane, mp 163-165°; ^{1}H nmr (deuteriochloroform): δ 1.05 (t, 3 H, J = 6.5 Hz, CH_3), 3.22-4.42 (m, 6 H, CH_2CH_2), 6.71 (s, 1 H, CH), 6.78-7.43 (m, 6 H, Ar), 7.60-7.98 (m, 2 H, Ar), 7.98 (s, 1 H, N=CH); ir (potassium bromide): 3080, 1715, 1620, 1480, 1310, 755 cm^{-1}.

Anal. Calcd. for $C_{22}H_{19}FN_4O_2S$: C, 62.55; H, 4.53; N, 13.26; S, 7.59. Found: C, 62.61; H, 4.55; N, 13.26; S, 7.71.

5-((1-Ethoxycarbonyl)-1,2-dihydro-2-quinolinyl)-6-(4-fluorophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (**6**) and 5-((1-Ethoxycarbonyl)-1,4-dihydro-4-quinolinyl)-6-(4-fluorophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (**7**).

The use of quinoline in this reaction afforded a 44% yield of a mixture of isomers **6** and **7** which were separated by column chormatography on Baker C18 silica gel (methanol:water, 3:1). Compound **6** was recovered in 19% yield after recrystallization from ethyl acetate-hexane, mp 194-196°; ^{1}H nmr (deuteriochloroform): δ 0.92 (t, 3 H, J = 7.0 Hz, CH_3), 3.05-4.22 (m, 6 H, CH_2CH_2, OCH_2), 6.90 (dd, 1 H, J = 10.0, 5.5 Hz, CH=C*H*CH), 6.37-6.65 (m, 2 H, C*H*=CHC*H*), 6.80-7.75 (m, 8 H, Ar); ir (potassium bromide): 1705, 1475, 1375, 1260, 1205, 830 cm^{-1}.

Anal. Calcd. for $C_{23}H_{20}FN_3O_2S$: C, 65.54; H, 4.78; N, 9.97; F, 4.51; S, 7.61. Found: C, 65.49; H, 4.84; N, 10.10; F, 4.57; S, 7.55.

Compound **7** was recovered in 13% yield after recrystallization from ethyl acetate-hexane, mp 194.5-196.5°; ^{1}H nmr (deuteriochloroform): δ 0.90 (t, 3 H, J = 7.0 Hz, CH_3), 3.05-4.22 (m, 6 H, CH_2CH_2, OCH_2), 6.90 (dd, 1 H, J = 10.0, 2.75 Hz, CH=C*H*CH), 6.37-6.65 (m, 2 H, C*H*=CHC*H*), 6.80-7.75 (m, 8 H, Ar); ir (potassium bromide): 2990, 1710, 1495, 1310, 845 cm^{-1}.

Anal. Calcd. for $C_{23}H_{20}FN_3O_2S$: C, 65.54; H, 4.78; N, 9.97; F, 4.51; S, 7.61. Found: C, 65.51; H, 4.65; N, 9.71; S, 7.57.

General Procedure for the Preparation of 5-(Heteroaromatic)-6-(4-fluorophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazoles **10**, **12**, **13**, **15** by Oxidation with *o*-Chloranil.

The precursor (3.0 mmoles) was dissolved in toluene (25 ml), treated with *o*-chloranil, (0.79 g, 3.2 mmoles), and heated to reflux until tlc showed the absence of starting material (30-90 minutes). After cooling, 10% aqueous sodium hydroxide and ethyl acetate were added, and the reaction was stirred for 10 minutes. The mixture was filtered through Celite, and the organic phase was washed with water and brine, and dried (anhydrous magnesium sulfate). The organic solvents were removed *in vacuo*, and the product was isolated by column chromatography on silica gel.

5-(1-Phthalazinyl)-6-(4-fluorophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (**10**).

Column chromatography (ethyl acetate) afforded a 32% yield of **10** after recrystallization from acetonitrile-hexane, mp 262-263°; ^{1}H nmr (deuteriochloroform): δ 3.67-4.07 (m, 2 H, CH_2), 4.18-4.57 (m, 2 H, CH_2), 6.53-6.93 (m, 2 H, Ar), 7.03-7.40 (m, 2 H, Ar), 7.45-8.03 (m, 4 H, Ar), 9.47 (s, 1 H, CH=N); ir (potassium bromide): 1500, 1410, 1225, 835, 755 cm^{-1}.

Anal. Calcd. for $C_{19}H_{13}FN_4S$: C, 65.50; H, 3.76; N, 16.08; F, 5.45; S, 9.20. Found: C, 65.32; H, 3.91; N, 16.27; F, 5.43; S, 9.10.

5-(4-Quinazolinyl)-6-(4-fluorophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (**12**).

Column chromatography (acetonitrile:methylene chloride, 1:9) afforded a 76% yield of **12** as a glass. ^{1}H nmr (deuteriochloroform): δ 3.70-4.07 (m, 2 H, CH_2), 4.18-4.60 (m, 2 H, CH_2), 6.50-8.13 (m, 8 H, Ar), 9.32 (s, 1 H, N-CH-N); ir (chloroform): 2985, 1570, 1505, 1410, 1235, 910, 840 cm^{-1}; hrms, m/z Calcd. for $C_{19}H_{13}FN_4S$: 348.08469. Found: 348.0858.

5-(2-Quinolinyl)-6-(4-fluorophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (**13**).

Column chromatography (diethyl ether:petroleum ether, 3:1) afforded a 49% yield of **13** after recrystallization from 2-propanol-hexane, mp 148-150°; ^{1}H nmr (deuteriochloroform): δ 3.70-4.07 (m, 2 H, CH_2), 4.53-4.90 (m, 2 H, CH_2), 6.82-8.13 (m, 10 H, Ar); ir (potassium bromide): 1595, 1495, 1425, 1215, 830, 755 cm^{-1}.

Anal. Calcd. for $C_{20}H_{14}FN_3S$: C, 69.14; H, 4.06; N, 12.10; F, 5.47; S, 9.23. Found: C, 69.33; H, 4.23; N, 12.22; F, 5.71; S, 9.28.

5-(4-(3-Bromoquinolinyl))-6-(4-fluorophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (**15**) and 5-((1-Ethoxycarbonyl)-1,2-dihydro-3-bromo-2-quinolinyl)-6-(4-fluorophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (**8**).

3-Bromoquinoline and ethyl chloroformate reacted with **1** according the general procedure. The crude product mixture of isomers **8** and **9** was treated with *o*-chloranil by the general procedure. Column chromatography (silica gel, ethyl acetate:hexane, 1:1) afforded **15** (R_f = 0.51) in 33% yield after recrystallization from toluene-hexane, mp 202-204°; ^{1}H nmr (deuteriochloroform): δ 3.53-4.10 (m, 4 H, CH_2CH_2), 6.55-6.97 (m, 2 H, Ar), 7.07-7.90 (m, 5 H, Ar), 8.03-8.27 (m, 1 H, Ar), 9.08 (s, 1 H, N-CH-CBr); ir (potassium bromide): 1505, 1490, 1460, 1330, 1230, 835, 755 cm^{-1}; hrms, m/z Calcd. for $C_{20}H_{13}BrFN_3S$: 426.0069; Found: 426.0069.

Anal. Calcd. for $C_{20}H_{19}BrFN_3S$: C, 56.35; H, 3.07; N, 9.86; Br, 18.74; S, 7.52. Found: C, 56.08; H, 3.13; N, 9.81; Br, 18.54; S, 7.44.

Compound **8** (R_f = 0.36) was recovered in 27% yield after recrystallization from acetonitrile-hexane, mp 224-225°. ^{1}H nmr (deuteriochloroform): δ 0.98 (t, 3 H, J = 8.0 Hz, CH_3), 3.03-4.20 (m, 6 H, CH_2CH_2, OCH_2), 6.55 (s, 1 H, NCHCBr), 6.73-7.75 (m, 9 H, Ar); ir (potassium bromide): 1705, 1485, 1380, 1285, 1230, 1055, 840 cm^{-1}.

Anal. Calcd. for $C_{23}H_{19}BrFN_3O_2S$: C, 55.21; H, 3.83; N, 8.40; F, 3.80; Br, 15.97; S, 6.41. Found: C, 55.50; H, 3.79; N, 8.49; F, 3.87; Br, 15.64; S, 6.32.

Preparation of 6-(4-Fluorophenyl)-5-(1-isoquinolinyl)-2,3-dihydroimidazo[2,1-*b*]thiazole, Dihydrochloride Hydrate (**11**) by Electrochemical Oxidation.

The anodic oxidation of **4** was carried out in a two compartment divided H-cell equipped with cylindrical coarse vitreous carbon anode and a saturated calomel reference electrode in the anode compartment and a graphite rod cathode in the cathode compartment. A solution of **4** (0.21 g, 0.5 mmole) in a mixture of acetonitrile (20 ml) and 0.5 *M* hydrochloric acid (20 ml) was added to the anode compartment and electrolized at +1.4 V vs. SCE (saturated calomel electrode). The controlled-potential electrolysis was monitored by tlc (methylene chloride-methanol-ammonium hydroxide, 9.5:0.5:0.1) until the reaction was complete. The time and current required for oxidation corresponded to the loss of 2.8 electrons per molecule. The yellow anolyte was concentrated *in vacuo*. The residue was dissolved in methanol (6 ml) and treated with gaseous hydrochloric acid. After cooling to 5°, acetone (40 ml) was added. The yellow crystalline product was collected by filtration and dried to give **11** (0.12 g, 57%), mp 222-224°; ^{1}H nmr (dimethyl sulfoxide-d_6 + deuterium oxide): δ 3.98-4.72 (m, 4 H, CH_2CH_2), 7.07-8.25 (m, 9 H, Ar), 8.76 (d, 1 H, J = 5.8 Hz, CH=N);. ir (potassium bromide): 1630, 1512, 1498, 1240, 837 cm^{-1}.

Anal. Calcd. for $C_{20}H_{14}FN_3S \cdot 2HCl \cdot 1/2H_2O$: C, 55.95; H, 3.87; N, 9.79. Found: C, 55.92; H, 4.04; N, 9.86.

Preparation of 5-(4-Quinolinyl)-6-(4-fluorophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (**14**) by Sulfur Oxidation.

The crude mixture of isomers **6** and **7** (2.11 g, 5.0 mmoles) was suspended in mesitylene (20 ml) and sulfur was added (0.32 g, 10.0 g-atoms). The reaction was heated to reflux for 2 hours. After cooling, the mesitylene was removed *in vacuo*, and the product, **14**, was isolated by column chromatography (silica gel, diethyl ether:petroleum ether, 3:1) in 55% yield as a hygroscopic glass; ^{1}H nmr (deuteriochloroform): δ 3.70-4.00 (m, 4 H, CH_2CH_2), 6.60-7.00 (m, 2 H, Ar), 7.13- 7.92 (m, 6 H, Ar), 8.07-8.33 (m, 1 H, Ar), 8.97 (d, 1 H, J = 4.0 Hz, CH=N); ir (chloroform): 2970, 1600, 1595, 1230, 910, 840 cm^{-1}; hrms, m/z Calcd. for $C_{20}H_{13}FN_3S$: 347.0901. Found: 347.0891. The residue was dissolved in methanol (6 ml) and treated with gaseous hydrogen chloride. After cooling to 5°, ethyl acetate (30 ml) was added. The yellow crystalline product was collected by filtration and dried to give **14** (0.75 g), mp 256-258°.

Anal. Calcd. for $C_{20}H_{14}FN_3S \cdot 2HCl \cdot 1/4H_2O$: C, 56.54; H, 3.91; N, 9.89; Cl, 16.69; F, 4.47; S, 7.55. Found: C, 56.63; H, 4.03; N, 9.80; Cl, 17.03; F, 4.31; S, 7.65.

Acknowledgment.

The authors wish to acknowledge their indebtedness to Ms. Edith Reich of the Analytical Chemistry department for elemental analyses and to the Mass Spectrometry Facility of the Physical and Structural Chemistry department for spectral data.

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