The Synthesis of 5-Arylpyrrolo[3,2-*b*]pyridines and 7-Arylpyrrolo[3,2-*b*]pyridines: Addition of 3-Aminopyrroles to Aryl Enaminones

Gary H. Birnberg*, William J. Fanshawe, Gerardo D. Francisco and Joseph W. Epstein

Cardiovascular and Central Nervous System Disease Research Section,
Medical Research Division, American Cyanamid Company,
Lederle Laboratories, Pearl River, New York 10965

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A series of 5-arylpyrrolo[3,2-*b*]pyridines **1** was synthesized by addition of 3-aminopyrroles to aryl enaminones. One example of a 7-arylpyrrolo[3,2-*b*]pyridine **2** was obtained as a minor product along with the 5-aryl isomer, by a modification of the reaction sequence.

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When we initiated this work our intention was to prepare 7-arylpyrrolo[3,2-*b*] pyridines **2** which are deaza analogs of the pyrazolo[1,5-*a*]pyrimidine ring system. Some compounds of this ring system are active in CNS screens indicative of anxiolytics [1,2] Figure 1.

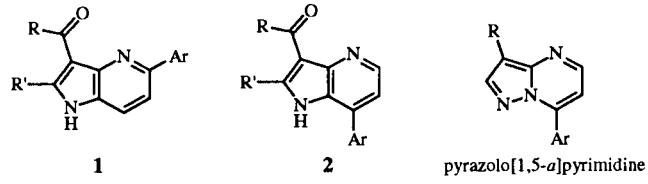
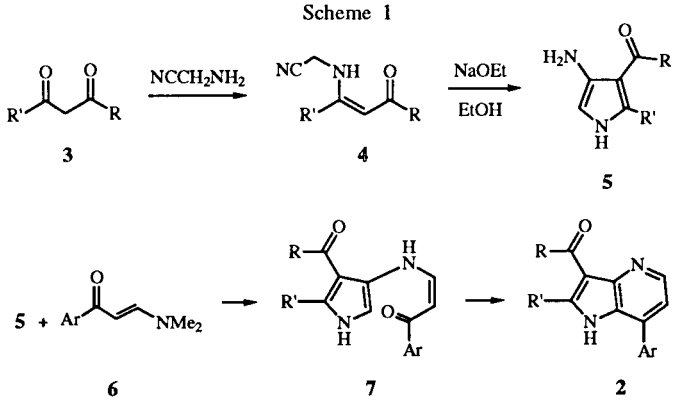


Figure 1

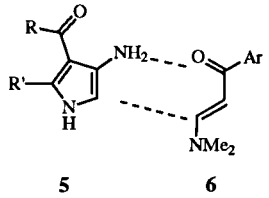
A search of the literature yielded only one reference to the synthesis of a 7-arylpyrrolo[3,2-*b*]pyridine, which was a report by Aumann [3] who prepared the 7-phenylpyrrolo[3,2-*b*]pyridine as the tungsten pentacarbonyl complex. However, this synthesis did not lend itself to the preparation of derivatives with the additional substituents in the desired pattern. The synthesis that we pursued is outlined in Scheme 1, and was based on the availability of β-aminopyrroles [4], their reaction with diethyl ethoxymethylenemalonate, and cyclization of the obtained intermediates to prepare 7-oxopyrrolo-[3,2-*b*]pyridine-6-carboxylic acids [5,6] and 6-carboethoxypyrrolo[3,2-*b*]pyridines [7]. We assumed that the addition of the aminopyrrole **5** to an arylenaminone **6** would occur in a manner analogous to the formation of pyrazolo[1,5-*a*]pyrimidines [1,2] and routes described by Sowell [5,6], to give an intermediate **7** that would then cyclize to form **2**.

Scheme 1



This reaction, however, proceeded by a mechanism involving the orientation shown in Scheme 2, which is similar to that seen for the addition of 2-nitro-1,1-diaminoethylene to aryl enaminones to give 2-amino-6-aryl-3-nitropyridines [8].

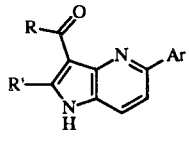
Scheme 2



The first set of reaction conditions used (method A), involved the evaporation of the alcohol solvent used in the generation of the aminopyrrole, replacement with acetic acid, and then addition of the enaminone followed by cyclization. An improved procedure (method B) avoided the replacement of solvent. Thus, acidification of the reaction mixture with two equivalents of acetic acid, followed by the addition of the enaminone gave the desired reaction. Table 1 lists the 5-arylpyrrolo[3,2-*b*]pyridines prepared by these procedures. These compounds could be alkylated with alkyl iodides under basic conditions. Those prepared are listed in Table 2. Hydrolysis of the *t*-butyl ester **8c** using *p*-toluenesulfonic acid in refluxing toluene yielded the decarboxylated 4-azaindole **8d** (Scheme 3).

Two possible mechanisms to explain the formation of the 5-isomer are shown in Scheme 4. Rather than the expected Michael addition which would yield the 7-aryl

Table 1

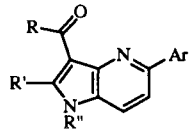


1

5-Arylpyrrolo[3,2-*b*]pyridines

Compound	Ar	R	R'	Mp, °C	Yield, %	Method	Enamine Used
1a	*m*-CF_3Ph	EtO	Me	171-172	18	A	**4c**
1b	*p*-CH_3Ph	EtO	Me	197-199	10	B	**4c**
1c	Ph	EtO	Me	174-175	16	A	**4c**
1d	*m*-CF_3Ph	Ph	Me	219-220	37	B	**4d**
1e	*m*-ClPh	EtO	Me	150-153	31	B	**4c**
1f	4-pyridyl	EtO	Me	280-286	16	B	**4c**
1g	*m*-CF_3Ph	EtO	Ph	190-191	28	B	**4e**
1h	*m*-CF_3Ph	*t*-BuO	Me	190-191	35	B	**4a**
1i	*m*-CF_3Ph	MeO	Me	170-171	61	B	**4b**

Table 2



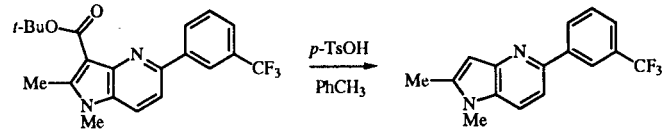
8

1-Alkyl-5-arylpyrrolo[3,2-*b*]pyridines

Compound	Ar	R	R'	R"
8a	*m*-CF_3Ph	EtO	Me	Et
8b	*m*-CF_3Ph	EtO	Me	Me
8c	*m*-CF_3Ph	*t*-BuO	Me	Me

isomer (pathway a), either the amine reacts directly with the ketone (pathway b) followed by cyclization, or the enaminone could react at the α-position of the pyrrole (pathway c) and then cyclize.

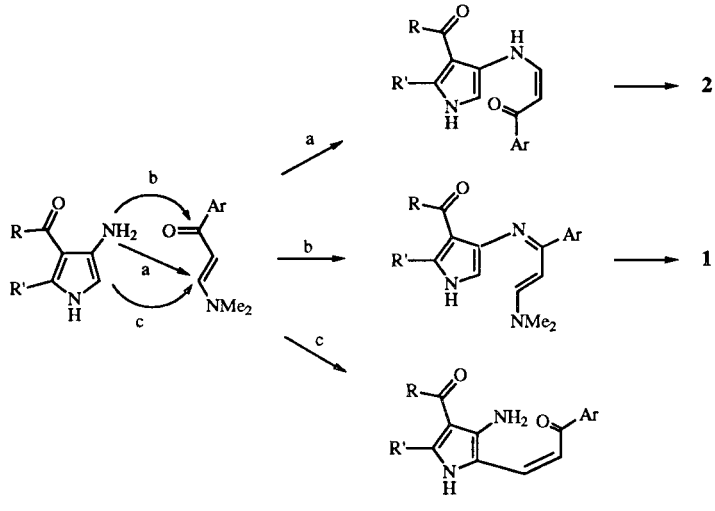
Scheme 3



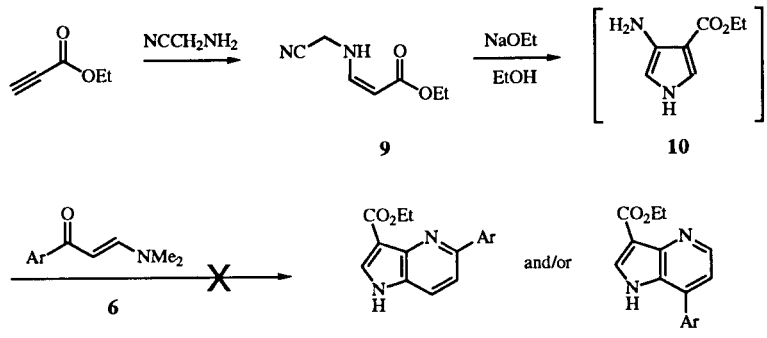
8c **8d**

The nmr spectra for the products isolated from this reaction were not consistent with those expected for 7-aryl substitution. The major discrepancy was the coupling constant between the two protons on the pyridine-ring-portion of the molecule. On the basis of an analogy with pyridine, the coupling constant between protons in the 5 and 6 positions should be 5-6 Hz. What we observed was a coupling constant of 8.5 Hz; this better suits coupling constants between protons in the 6 and 7 positions. The other was the chemical shift for the proton in what was assigned as the "5-position" at δ 7.65 (deuteriochloro-

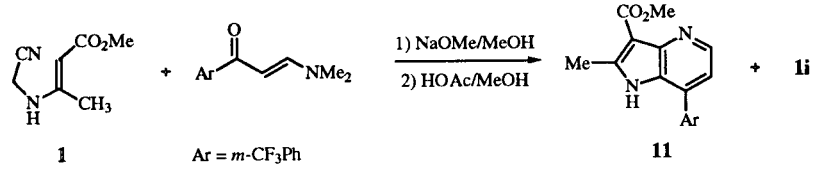
Scheme 4



Scheme 5



Scheme 6



form). Comparison with the parent ring system, in which the proton at the 5-position is reported [9] at δ 8.39 (perdeuteriomethanol) and that of the 7-position at δ 7.64, indicated that the structure of the products obtained be assigned as **1** [10].

Attempts to prepare derivatives that are unsubstituted in the 2-position were unsuccessful (Scheme 5). The intermediate **9** could be prepared and isolated, however, conversion in the usual manner to a pyrrolo[3,2-*b*]pyridine failed. It seemed likely that the cyclization to the pyrrole **10** was the problem, or that the pyrrole was unstable. Incorporation of the enaminone into the reaction mixture during the formation of the pyrrole to trap it as soon as it was formed, likewise, did not yield any pyrrolo[3,2-*b*]pyridine.

The 7-aryl isomer **11** was prepared (Scheme 6), as the minor component, along with the 5-aryl isomer **1i** in a ratio of approximately 1:2.5 by including the enaminone in the reaction mixture (method C) in which the β-aminopyrrole **5** was being generated, followed by acidification and continued reaction in the usual manner. Extension of these reactions to other heterocyclic systems will follow.

EXPERIMENTAL

All melting points were taken on a Thomas-Hoover apparatus in open capillary tubes, and are uncorrected. The nmr spectra were run on a General Electric QE-300 spectrometer. Chemical shifts are reported rounded to the nearest hundredth of a ppm and coupling constants are rounded to the nearest tenth of a hertz.

t-Butyl 3-(Cyanomethyl)amino-2-buten-1-oate (**4a**).

A mixture of 50.21 g (0.553 mole) of aminoacetonitrile hydrochloride, 46.5 g (0.553 mole) of sodium bicarbonate and 500 ml of absolute ethanol was stirred for 30 minutes at ambient temperature. To this stirred mixture was added 500 ml of toluene and 81.0 g (0.512 mole) of *t*-butyl acetoacetate, the mixture was heated at reflux for three hours. The solvent was removed by distillation until the temperature of the distillate was 110°. The reaction mixture was filtered through celite and the pad rinsed with toluene, the filtrate was allowed to stand overnight, a small amount of brown residue was deposited, and the supernatant was filtered through a pad of magnesol. The clarified filtrate was evaporated to near dryness and the oil treated with hexanes. The resulting solid was isolated by suction, washed with hexanes and air dried to give **4a** as an off-white solid 28.59 g (26% yield), mp 55-57°; ^{1}H nmr (deuteriochloroform): δ 1.46 (s, 9H, *t*-Bu), 2.01 (s, 3H, CH_3), 4.09 (d, J = 6.8 Hz, 2H, CH_2), 4.64 (s, 1H, CH), 8.68 (br, 1H, NH).

Anal. Calcd. for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.27. Found: C, 60.73; H, 7.85; N, 14.40.

Methyl 3-(Cyanomethyl)amino-2-buten-1-oate (**4b**).

A mixture of 92.5 g (1.0 mole) of aminoacetonitrile hydrochloride, 84.4 g (1.04 mole) of sodium bicarbonate and 1000 ml of absolute ethanol was stirred for 15 minutes at ambient temperature. To this stirred mixture was added 2000 ml of toluene and 118.4 g (1.02 mole) of methyl acetoacetate, and this was heated at reflux for three hours. The solvent was then removed by distillation until the volume in the flask was 300 ml. The reaction mixture was filtered hot through celite to remove suspended solids. The filtrate was evaporated *in vacuo*, no solid forms. A mixture of 150 ml of toluene and 150 ml of cyclohexane was added and the mixture cooled. The crystals that formed were filtered, rinsed with fresh solvent and air dried, to give 124.18 g of **4b** as a white solid, mp 82-83°; ^{1}H nmr (deuteriochloroform): δ 2.05 (d, J = 0.7 Hz, 3H, CH_3), 3.65 (s, 3H, OCH_3), 4.12 (d, J = 6.8 Hz, 2H, CH_2N), 4.72 (d, J = 0.7 Hz, 1H, CH), 8.66 (bm, 1H, NH).

Anal. Calcd. for $C_7H_{10}N_2O_2$: C, 54.54; H, 6.54; N, 18.17. Found: C, 54.59; H, 6.37; N, 18.17.

Ethyl 3-(Cyanomethyl)amino-2-buten-1-oate (**4c**).

A mixture of 46.25 g (0.5 mole) of aminoacetonitrile hydrochloride, 42.2 g (0.502 mole) of sodium bicarbonate and 1000 ml of absolute ethanol was stirred for 15 minutes at ambient temperature. To this stirred mixture was added 1000 ml of toluene and 65.07 g (0.50 mole) of ethyl acetoacetate, the mixture then heated at reflux for three hours, then concentrated by distillation to a volume of 300 ml. The reaction mixture was filtered hot through celite to remove suspended solids. The filtrate was evaporated *in vacuo* until solid formed. This mixture was cooled and filtered. The solids were rinsed with fresh solvent and air dried to give 54.84 g (56%) of **4c** as a white solid, mp 92-93°; A second crop was obtained after concentration of the filtrate, 15.78 g (16% yield); ^{1}H nmr (deuteriochloroform): δ 1.26 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 2.05 (d, J = 0.7 Hz, 3H, CH_3), 4.11 (q, J = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.12 (d, J = 6.7 Hz, 2H, CH_2N), 4.71 (d, J = 0.7 Hz, 1H, CH), 8.30 (bm, 1H, NH); lit ref [4], mp 92-94°.

1-Phenyl 3-(Cyanomethyl)amino-2-buten-1-one (**4d**).

A mixture of 8.72 g (0.156 mole) of aminoacetonitrile, 25.22 g (0.156 mole) of benzoylacetone, and 300 ml of toluene was heated to reflux and water was removed by using a Dean-Stark trap. The reaction mixture was filtered hot through celite to remove suspended solids, and rinsed with 75 ml of hot toluene. The filtrate was cooled to room temperature, the product precipitated, and was collected to give 13.6 g of **4d** as a solid, mp 107-108°; second crop after concentration of the filtrate, 9.57 g (total yield 74%); ^{1}H nmr (deuteriochloroform): δ 2.21 (s, 3H, CH_3), 4.22 (d, J = 6.6 Hz, 2H, CH_2N), 5.89 (s, 1H, CH), 7.44 (m, 3H); 7.86 (m, 2H), 11.33 (bm, 1H, NH); lit ref [4], mp 102-104°, lit ref [6], mp 109-110°.

Ethyl 3-(Cyanomethyl)amino-3-phenyl-2-propen-1-oate (**4e**).

A mixture of 46.25 g (0.5 mole) of aminoacetonitrile hydrochloride, 42.2 g (0.502 mole) of sodium bicarbonate and 1000 ml of absolute ethanol was stirred for 15 minutes at ambient temperature. To this stirred mixture was added 1000 ml of toluene and 96.10 g (0.50 mole) of ethyl benzoylacetate, and this mixture was heated at reflux for three hours, solvent was removed by distillation until the volume in the flask was approximately 300 ml. The reaction mixture was filtered hot through celite to remove suspended solids. The mixture was then evaporated to give an orange oil, 94.5 g. This turned out to be a mixture of unreacted keto-ester and the desired enamine, which was isolated from the mixture by preparative hplc eluting with 5:1 hexane/ethyl acetate on silica gel as an off white solid mp 51-52° in 30% isolated yield; ^{1}H nmr (deuteriochloroform): δ 1.30 (t, J = 7.1 Hz, 3H, CH_2CH_3), δ 3.94 (d, J = 7.0 Hz, 2H, CH_2N), 4.18 (q , J = 7.1 Hz, 2H, CH_2CH_3), 4.91 (s, 1H, CH), 7.44 (m, 5H, Ph), 8.62 (bm, 1H, NH).

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.63; H, 6.13; N, 11.83.

General Procedures for the Preparation of 4-Azaindoles.

Method A.

The pyrrole precursor **4** was treated with 1.1 equivalents of sodium ethoxide (prepared fresh from sodium and ethanol), stirred for 1 hour at 60°, cooled to ambient temperature, then the solvent was removed *in vacuo*. Acetic acid was added as the new solvent, followed by addition of the enaminone (0.9 equivalent). The mixture was heated overnight, then worked up by evaporating the reaction mixture *in vacuo*, and partitioning between chloroform and saturated sodium bicarbonate solution. The organic layer was purified by chromatography on silica gel to give the product.

Method B.

The pyrrole precursor **4** was treated with 1.1 equivalents of sodium methoxide, stirred for 1 hour at 60°, cooled in an ice bath, then 2 equivalents of acetic acid were added, followed by addition of the enaminone. The mixture was heated overnight at reflux, then worked up by evaporating the reaction mixture *in vacuo*, and partitioning between chloroform and saturated sodium bicarbonate solution. The organic layer was purified by chromatography on silica gel to give the product.

Method C.

The pyrrole precursor **4** and the enaminone (0.9 equivalent) were treated with 1.1 equivalents of sodium methoxide stirred for 1 hour at 60°, cooled in an ice bath, then 2 equivalents of acetic acid were added. The mixture was heated overnight at reflux, then worked up by evaporating the reaction mixture *in vacuo*, and partitioning between chloroform and saturated sodium bicarbonate solution. The organic layer was purified by chromatography on silica gel to give the product.

3-Carboethoxy-2-methyl-5-(3-trifluoromethylphenyl)pyrrolo-[3,2-*b*]pyridine (**1a**).

The product was obtained using method A, and crystallized from toluene, yield 18%, mp 171-172°; ^{1}H nmr (deuteriochloroform): δ 1.47 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 2.71 (s, 3H, CH_3), 4.44 (q , J = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 7.44 (t, J = 7.8 Hz, 1H, H5'), 7.53 (d, J = 8.5 Hz, 1H, H6), 7.54 (d, J = 7.9 Hz, 1H, H4'), 7.57 (d, J = 8.5 Hz, 1H, H7), 8.16 (d, J = 7.8 Hz, 1H, H6'), 8.40 (s, 1H, H2'), 9.58 (bs, 1H, NH).

Anal. Calcd. for $C_{18}H_{15}F_3N_2O_2$: C, 62.07; H, 4.34; F, 16.36; N, 8.04. Found: C, 62.10; H, 4.20; F, 16.75; N, 7.97.

3-Carboethoxy-2-methyl-5-(4-methylphenyl)pyrrolo[3,2-*b*]-pyridine (**1b**).

The product was obtained using method B, and crystallized from toluene, yield 10%, mp 197-199°; ^{1}H nmr (deuteriochloroform): δ 1.45 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 2.35 (s, 3H, 4'-CH_3), 2.68 (s, 3H, 2-CH_3), 4.42 (q, J = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 7.45 (d, J = 8.0 Hz, 2H, H3' & H5'), 7.51 (d, J = 8.5 Hz, 1H, H6), 7.56 (d, J = 8.5 Hz, 1H, H7), 7.96 (d, J = 7.9 Hz, 2H, H6' & H2'), 8.74 (bs, 1H, NH).

Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.14; H, 6.11; N, 9.42.

3-Carboethoxy-2-methyl-5-phenylpyrrolo[3,2-*b*]pyridine (**1c**).

The product was obtained using method A, and crystallized from toluene, yield 19%, mp 174-175°. ^{1}H nmr (deuteriochloroform) δ 1.44 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 2.64 (s, 3H, CH_3), 4.40 (q, J = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 7.26-7.40 (m, 3H, H3', H4' & H5'), 7.50 (d, J = 8.5 Hz, 1H, H6), 7.54 (d, J = 8.5 Hz, 1H, H7), 8.01-8.05 (m, 2H, H2' & H6'), 9.55 (bs, 1H, NH).

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.77; H, 5.63; N, 9.79.

3-Benzoyl-2-methyl-5-(3-trifluoromethylphenyl)pyrrolo[3,2-*b*]-pyridine (**1d**).

The product was obtained using method B, and crystallized

from toluene, yield 37%, mp 219-220°; ^{1}H nmr (deuteriochloroform): δ 2.87 (s, 3H, CH_3), 7.42-7.45 (m, 4H, H5', 3 Ph H), 7.63 (d, J = 8.5 Hz, 1H, H6, overlap with H4'), 7.63-7.67 (m, 1H, H4', overlap with H6), 7.71 (d, J = 8.5 Hz, 1H, H7), 7.93-7.98 (m, 3H, H6', 2 Ph H), 8.04 (s, 1H, H2'), 8.57 (bs, 1H, NH).

Anal. Calcd. for $C_{22}H_{15}F_3N_2O$: C, 69.47; H, 3.97; F, 14.98; N, 7.36. Found: C, 69.48; H, 4.05; F, 14.72; N, 7.32.

3-Carboethoxy-2-methyl-5-(3-chlorophenyl)pyrrolo[3,2-*b*]pyridine (**1e**).

The product was obtained using method B, and crystallized from toluene, yield 31%, mp 150-153°; ^{1}H nmr (deuteriochloroform): δ 1.48 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 2.71 (s, 3H, CH_3), 4.43 (q , J = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 7.23-7.32 (m, 2H, H5' & H4'), 7.48 (d, J = 8.2 Hz, 1H, H6), 7.55 (d, J = 8.2 Hz, 1H, H7), 7.85-7.91 (m, 1H, H6'), 8.09 (s, 1H, H2'), 9.53 (bs, 1H, NH).

Anal. Calcd. for $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.80; Cl, 11.26; N, 8.90. Found: C, 64.52; H, 4.84; Cl, 11.56; N, 8.65.

3-Carboethoxy-2-methyl-5-(4-pyridyl)pyrrolo[3,2-*b*]pyridine (**1f**).

The product was obtained using method B, and crystallized from 2-propanol, yield 16%, mp 280-286° dec; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.40 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 2.72 (s, 3H, 2-CH_3), 4.31 (q , J = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 7.86 (d, J = 8.5 Hz, 1H, H6), 7.94 (d, J = 8.5 Hz, 1H, H7), 8.14-8.17 (m, 2H, H6' & H2'), 8.65-8.68 (m, 2H, H5' & H3'), 12.20 (bs, 1H, NH).

Anal. Calcd. for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 67.84; H, 5.55; N, 14.73.

3-Carboethoxy-2-phenyl-5-(3-trifluoromethylphenyl)pyrrolo-[3,2-*b*]pyridine (**1g**).

The product was obtained using method B, and crystallized from acetonitrile, yield 28%, mp 190-191°; ^{1}H nmr (deuteriochloroform): δ 1.42 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 4.38 (q, J = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 7.41-7.47 (m, 3H, 3 Ph H), 7.56 (t, J = 7.7 Hz, 1H, H5'), 7.60-7.68 (m, 3H, H4', 2 Ph H), 7.69 (d, J = 8.5 Hz, 1H, H6), 7.76 (d, J = 8.5 Hz, 1H, H7), 8.30 (d, J = 7.7 Hz, 1H, H6'), 8.50 (s, 1H, H2'), 8.85 (bs, 1H, NH).

Anal. Calcd. for $C_{23}H_{17}F_3N_2O_2$: C, 67.31; H, 4.18; F, 13.89; N, 6.83. Found: C, 67.19; H, 4.05; F, 13.86; N, 6.80.

3-(Carbo-*t*-butoxy)-2-methyl-5-(3-trifluoromethylphenyl)-pyrrolo[3,2-*b*]pyridine (**1h**).

The product was obtained using method B, and crystallized from toluene/cyclohexane, yield 35%, mp 190-191°; ^{1}H nmr (deuteriochloroform): δ 1.71 (s, 9H, CO_2t-Bu), 2.75 (s, 3H, CH_3), 7.49 (t, J = 7.7 Hz, 1H, H5'), 7.55-7.65 (m, 3H, H6, H7 & H4'), 8.24 (d, J = 7.7 Hz, 1H, H6'), 8.50 (s, 1H, H2'), 8.89 (bs, 1H, NH).

Anal. Calcd. for $C_{20}H_{19}F_3N_2O_2$: C, 63.82; H, 5.09; F, 15.14; N, 7.44. Found: C, 63.61; H, 5.32; F, 14.83; N, 7.22.

3-Carbomethoxy-2-methyl-5-(3-trifluoromethylphenyl)pyrrolo-[3,2-*b*]pyridine (**1i**).

The product was obtained using method B, and crystallized from ethyl acetate to yield 61%, mp 170-171°; ^{1}H nmr (deuteriochloroform): δ 2.70 (s, 3H, CH_3), 3.96 (s, 3H, CO_2CH_3), 7.45 (t, J = 7.7 Hz, 1H, H5'), 7.53 (d, J = 8.5 Hz, 1H, H6), 7.55 (d, J = 7.7 Hz, 1H, H4'), 7.59 (d, J = 8.5 Hz, 1H, H7), 8.18 (d, J = 7.7 Hz, 1H, H6'), 8.29 (s, 1H, H2'), 9.59 (bs, 1H, NH).

The analytical sample was recrystallized from toluene.

Anal. Calcd. for $C_{17}H_{13}F_3N_2O_2$: C, 61.08; H, 3.92; F, 17.05; N, 8.38. Found: C, 61.33; H, 4.03; F, 17.34; N, 8.19.

3-Carbomethoxy-2-methyl-7-(3-trifluoromethylphenyl)pyrrolo-[3,2-*b*]pyridine (**11**).

The product was obtained using method C, and crystallized from acetonitrile, yield 24%, mp 285-290° dec; ^{1}H nmr (deuteriochloroform): δ 2.82 (s, 3H, CH_3), 4.02 (s, 3H, CO_2CH_3), 7.16 (d, J = 5.0 Hz, 1H, H6), 8.66 (d, J = 5.0 Hz, 1H, H5), 7.67 (t, J = 7.6 Hz, 1H, H5'), 7.74 (d, J = 7.9 Hz, 1H, H4'), 7.80 (d, J = 7.5 Hz, 1H, H6'), 7.67 (s, 1H, H2'), 8.83 (bs, 1H, NH).

Anal. Calcd. for $C_{17}H_{13}F_3N_2O_2$: C, 61.08; H, 3.92; F, 17.05; N, 8.38. Found: C, 60.84; H, 4.02; F, 16.76; N, 8.27.

Compound **1i** was also obtained in 56% yield.

3-Carboethoxy-1-ethyl-2-methyl-5-(3-trifluoromethylphenyl)-pyrrolo[3,2-*b*]pyridine (**8a**).

To a mixture of 1.30 g (3.73 mmoles) of the indole ester, 20 ml of dimethylformamide and 1.55 g (11.21 mmoles) of potassium carbonate was added 1.75 g (11.21 mmoles) of ethyl iodide. This was stirred and heated at 65° overnight in an oil bath. The solvent was removed *in vacuo* and the residue was taken up in chloroform and passed through a short pad of silica gel and magnesol, eluting with chloroform. The resulting orange eluate was evaporated and then chromatographed on silica gel eluting with hexanes/ethyl acetate 2:1. The product was recrystallized from cyclohexane to give 1.16 g (82%) of **8a** as a yellow solid, mp 104-105°; ^{1}H nmr (deuteriochloroform): δ 1.41 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.57 (t, J = 7.2 Hz, 3H, NCH_2CH_3), 2.86 (s, 3H, 2-CH_3), 4.23 (q, J = 7.3 Hz, 2H, NCH_2CH_3), 4.48 (q , J = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 7.54-7.65 (m, 2H, H4' & H5'), 7.67 (d, J = 8.5 Hz, 1H, H6), 7.69 (d, J = 8.5 Hz, 1H, H7), 8.30 (d, J = 7.4 Hz, 1H, H6'), 8.57 (s, 1H, H2').

Anal. Calcd. for $C_{20}H_{19}F_3N_2O_2$: C, 63.82; H, 5.09; F, 15.14; N, 7.44. Found: C, 63.90; H, 5.15; F, 15.18; N, 7.32.

3-Carboethoxy-1,2-dimethyl-5-(3-trifluoromethylphenyl)-pyrrolo[3,2-*b*]pyridine (**8b**).

A mixture of 1.04 g (3.0 mmoles) of **1a**, 1.24 g (9.0 mmoles) of potassium carbonate, 1.9 ml of iodomethane (30.0 mmoles) and 30 ml of dimethylformamide was heated at 90° (oil bath temp) for 20 hours. The reaction mixture was concentrated *in vacuo*, the solid residue was washed with 50 ml of water, extracted with dichloromethane, dried over sodium sulfate, filtered through magnesol and concentrated to give 0.8 g of a brown solid which was recrystallized to give 0.30 g of **8b** as a yellow solid, 27%, mp 152-154°. A second crop (tlc virtually the same as for the first crop, 3:1 hexanes/ethyl acetate) was obtained by adding 35 ml of hexanes to the mother liquor, 0.28 g (25%), mp 145-147°; ^{1}H nmr (deuteriochloroform): δ 1.57 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 2.80 (s, 3H, 2-CH_3), 3.71 (q , J = 7.3 Hz, 3H, (NCH_3)), 4.47 (q , J = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 7.51-7.75 (m, 4H, H6, H7, H4' & H5'), 8.28 (d, J = 7.6 Hz, 1H, H6'), 8.57 (s, 1H, H2').

Anal. Calcd. for $C_{19}H_{17}F_3N_2O_2$: C, 62.98; H, 4.73; F, 15.73; N, 7.73. Found: C, 62.55; H, 4.72; F, 15.42; N, 7.54.

3-(Carbo-*t*-butoxy)-1,2-dimethyl-5-(3-trifluoromethylphenyl)-pyrrolo[3,2-*b*]pyridine (**8c**).

A mixture of 5.27 g (14.0 mmoles) of **1h**, 5.80 g (42.0

mmoles) of potassium carbonate, 6.76 g (48.0 mmoles) of methyl iodide and 50 ml of acetone were refluxed until tlc showed that the starting indole was consumed. The reaction mixture was filtered, evaporated and the residue purified by column chromatography on silica gel, eluting with 3:1 hexanes/ethyl acetate, to give 4.2 g (61%) of **8c** as a pale yellow solid, mp 178-179°; ^{1}H nmr (deuteriochloroform): δ 1.74 (s, 9H, *t*-Bu), 2.83 (s, 3H, CH_3), 3.74 (s, 3H, CH_3), 7.56 (t, J = 7.7 Hz, 1H, H5'), 7.62 (d, J = 7.7 Hz, 1H, H4'), 7.64 (d, J = 8.5 Hz, 1H, H6), 7.68 (d, J = 8.5 Hz, 1H, H7), 8.31 (d, J = 7.5 Hz, 1H, H6'), 8.61 (s, 1H, H2').

Anal. Calcd. for $C_{21}H_{21}F_3N_2O_2$: C, 64.61; H, 5.42; F, 14.60; N, 7.18. Found: C, 64.54; H, 5.36; F, 14.23; N, 7.10.

1,2-Dimethyl-5-(3-trifluoromethylphenyl)pyrrolo[3,2-*b*]pyridine (**8d**).

A mixture of 1.95 g (5.0 mmoles) of 3-carbo-*t*-butoxy-1,2-dimethyl-5-(3'-trifluoromethylphenyl)pyrrolo[3,2-*b*]pyridine, 0.25 g (1.3 mmoles) of *p*-toluenesulfonic acid hydrate and 30 ml of toluene was heated at reflux for one day. After the reflux period, the solution was cooled and treated with saturated sodium bicarbonate solution (30 ml). This was filtered to remove solids, and the residue was washed with ether. The organic layer was isolated, dried over sodium sulfate, treated with magnesol, filtered and evaporated. The residue was crystallized from methylcyclohexane. The solid was isolated by filtration and rinsed with fresh solvent to give 1.06 g (73%) of **8d** as a pale yellow solid, mp 94-95°; ^{1}H nmr (deuteriochloroform): δ 2.51 (d, J = 0.9 Hz, 3H, CH_3), 3.71 (s, 3H, NCH_3), 6.53 (d, J = 0.9 Hz, 1H, H3), 7.52 (d, J = 8.5 Hz, 1H, H6), 7.60 (d, J = 8.5 Hz, 1H, H7), 7.53-7.63 (m, (overlap with H6 and H7), H5', H4'), 8.23 (d, J = 7.4 Hz, 1H, H6'), 8.30 (s, 1H, H2').

Anal. Calcd. for $C_{16}H_{13}F_3N_2$: C, 66.20; H, 4.51; F, 19.63; N, 9.65. Found: C, 66.12; H, 4.50; F, 19.60; N, 9.52.

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