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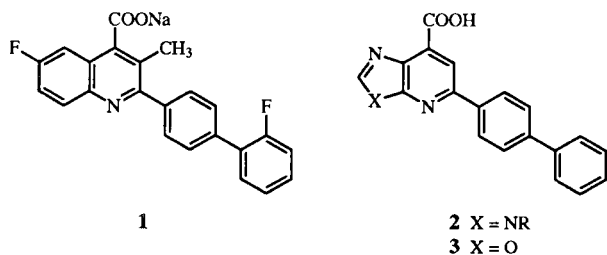
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Nitroacetamidine undergoes a useful cyclocondensation with β -diketones to produce substituted 2-amino-3-nitropyridines. Use of an acylpyruvate generates hitherto unreported 2-amino-3-nitropyridine-4-carboxylates. These may be converted easily to functionalized imidazo[4,5-*b*]pyridines and oxazolo[5,4-*b*]pyridines.

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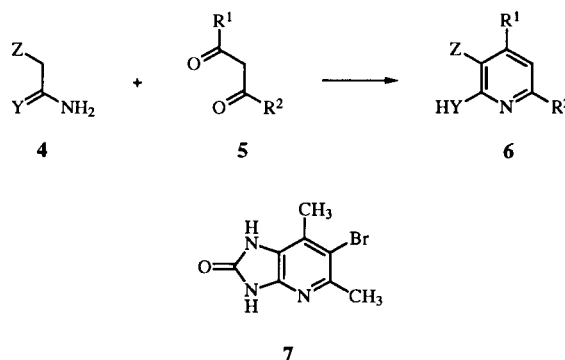
In the course of exploring novel analogs of Brequinar (1), a potent immunosuppressive drug under clinical evaluation for the inhibition of organ transplant rejection [1,2], we needed to prepare cinchoninic acid analogs in which the benzo ring is replaced by a 5-membered heterocyclic ring, such as the imidazo[4,5-*b*]pyridine and oxazolo[5,4-*b*]pyridine derivatives 2 and 3. Imidazo[4,5-*b*]pyridine-7-carboxylates are almost unknown in the literature: two papers reported the introduction of the acid functionality by oxidation of a 7-methylimidazo[4,5-*b*]pyridine [3,4], and in a third paper the carboxyl-bearing pyridine ring was annelated in low yield onto an amino-imidazole [5]. Only one example of an oxazolo[5,4-*b*]pyridine-7-carboxylate has been reported [6].



Imidazo[4,5-*b*]pyridines have most often been prepared by condensation of a 2,3-diaminopyridine with a carboxylic acid equivalent [7]. However, 2,3-diamino-4-pyridinecarboxylic acid derivatives appear to be unreported in the literature. One useful approach to substituted pyridines is the Guareschi synthesis (Scheme 1), which commonly provides 2-pyridones 6 (Y = O) by condensation of a β -diketone 5 or an equivalent with an activated amide 4 (Y = O), but has also yielded 2-aminopyridines 6 (Y = NH) by condensation with an amidine 4 (Y = NH) or two equivalents of an imideate [8]. The electron-withdrawing group Z is normally carbon-based (a nitrile, ester, amide or ketone), leading to a carbon 3-substituent on the product pyridine. In one reported case, the amide 3-sub-

stituent of 6 (Y = NH, Z = CONH₂) was converted by a Hofmann rearrangement to the isocyanate 6 (Y = NH, Z = NCO), which was trapped intramolecularly by the 2-amino group to give the corresponding 2-hydroxyimidazo[4,5-*b*]pyridine derivative 7, but only in low yield [9]. The direct formation of a 2,3-diaminopyridine derivative was reported by Uchida *et al.* [10], using *N*-acylaminoacetamidine as the nitrogen-containing fragment 4 (Y = NH, Z = acylamino), but again a very low yield was obtained.

Scheme 1



The nitrogen 3-substituent would be more efficiently introduced as a nitro group, which would provide the electron withdrawal required for the condensation of 4 with a diketone to occur. The synthesis of 3-nitropyridones from nitroacetamide has been reported previously [11,12]. The 2-hydroxyl could then be converted to an amino group; a related approach was used to prepare various *N*-substituted imidazo[4,5-*b*]pyridines by a rather long synthetic route [13]. A more direct approach, which would yield 2-amino-3-nitropyridine derivatives directly, was chosen for exploration, using nitroacetamidine 4 (Z = nitro, Y = NH) as the nucleophile. Shortly after this work was begun, one example of the condensation of nitroac-

etamidine with a diketone appeared [14]. The same workers have also used this reagent and substituted analogs with other 1,3-bis-electrophiles to prepare various 3-nitro-2-aminopyridines and -1,4-dihydropyridines [15,16], but none with a carboxyl substituent.

Nitroacetamidine (**8**) was prepared from nitroacetoneitrile [17] according to a literature procedure [18,19]. In contrast to the findings of Mertens and Troschütz [20], in our hands this material appeared to exist mostly as the amidine tautomer by nmr, with only a minor trace of the ketene aminal form observed.

In order to directly incorporate the biphenyl and carboxyl moieties desired in **2** and **3**, the biphenylcarbonylpyruvate ester **9a**, prepared by a literature method [21], was used as the diketone starting material. This was condensed with **8** in boiling ethanol, in the absence of any catalyst, to provide good yields of the desired nitroaminopyridine ester **10a**. Of the two possible regioisomers, only that shown was obtained; this is the isomer expected from addition of the active methylene of **8** to the more reactive α -carbonyl of **9a** [8]. None of the alternative isomer **11a** was detected. Preparation of the analogous diketone starting material with a methyl substituent at the β -carbon, **9b**, proved very difficult, in agreement with a literature report [22]. In this case, the diketone was obtained in only low yield and used directly as a crude mixture in the condensation with **8** to give **10b**.

The Guareschi condensation of nitroacetamidine with diketones was examined further to explore its generality

for preparing a variety of substituted 3-nitro-2-aminopyridines. α,γ -Diketone esters reacted quite readily in the absence of catalyst in boiling ethanol, giving generally good yields. Ethyl diketovalerate was particularly reactive, providing an excellent yield of **10c** after only 45 minutes. Trifluoromethyl ketones also provided acceptable yields of pyridine products **10d** and **10e**, but more sluggishly. Acetylacetone formed the desired product **10f**, as reported previously [14], but again somewhat more slowly. It appears that increased polarization of one of the ketones causes greater reactivity, as expected for nucleophilic attack on the carbonyl by the methylene of **8** as the first step in the condensation.

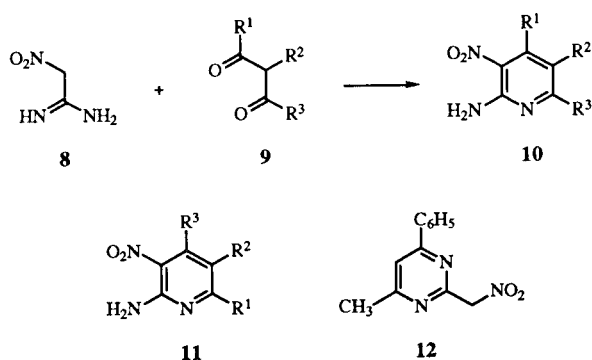
Benzoylacetone, on the other hand, reacted only poorly, giving low yields of **10h** after extended heating. No product at all resulted upon changing the solvent to acetic acid or *N,N*-dimethylformamide. Dibenzoylmethane could not be induced to react with nitroacetamidine at all; only starting material was recovered from numerous attempts. An attempt to activate the latter diketone system by polarizing it (as 4-methoxy-4'-nitrodibenzoylmethane [23]) was likewise unsuccessful.

We examined the action of catalysts on the condensation with benzoylacetone, attempting to improve the outcome of that reaction, and found some interesting effects. Addition of pyridinium acetate afforded both the expected compound **10h** and the other regioisomer **11h**, although both were obtained in low yield. This is the only case in which the alternative regioisomer **11** was detected. Piperidinium acetate surprisingly gave the pyrimidine **12**, although in low yield; this reaction course was not seen in any other reactions studied, although competing pyrimidine formation has sometimes been reported for the condensation of other amidines with diketones [24-27]. Possibly the catalyst affects the tautomeric form of the nitroacetamidine, altering the reactivity of the molecule and leading to other products.

Formylacetophenone was another interesting case, which provided the desired pyridine product **10g** only when the acid form of the ketoaldehyde was used. Attempts to condense the more commonly used sodium salt with **8** gave only recovered starting material. This reaction was very sensitive to catalysis as well: when the sodium salt was neutralized *in situ* with acetic acid, only a low yield (19%) was obtained, while ethereal hydrogen chloride provided the product in 60% yield. When the same reaction was attempted in the presence of piperidinium acetate, as suggested by the literature for related condensations [12,28], no reaction resulted.

The polysubstituted pyridine derivatives **10a** and **10b** were easily converted to the corresponding imidazo-[4,5-*b*]pyridines **14** by catalytic reduction of the nitro group and condensation with orthoesters, as shown in

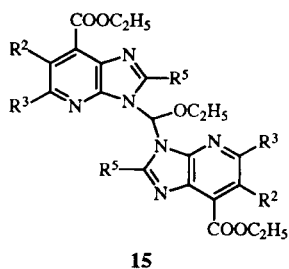
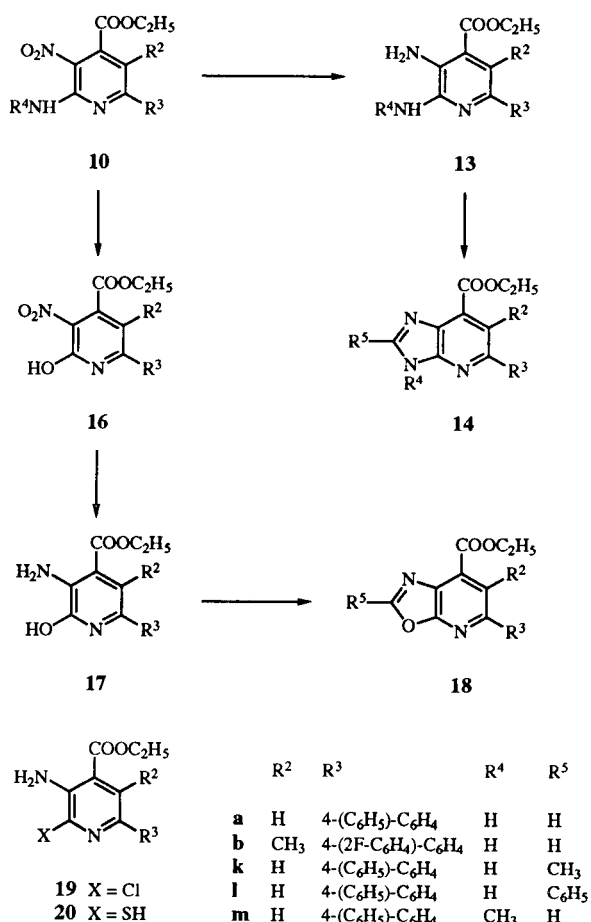
Scheme 2



	R ¹	R ²	R ³
a	COOC ₂ H ₅	H	4-(C ₆ H ₅)-C ₆ H ₄
b	COOC ₂ H ₅	CH ₃	4-(2F-C ₆ H ₄)-C ₆ H ₄
c	COOC ₂ H ₅	H	CH ₃
d	CF ₃	H	C ₆ H ₅
e	CF ₃	H	CH ₃
f	CH ₃	H	CH ₃
g	H	H	C ₆ H ₅
h	CH ₃	H	C ₆ H ₅
i	C ₆ H ₅	H	C ₆ H ₅
j	4-NO ₂ -C ₆ H ₄	H	4-CH ₃ O-C ₆ H ₄

Scheme 3. Although the intermediate diaminopyridines **13** could be purified, the crude products were suitable for further reaction. Side-products of the condensation with the orthoesters were the bis-condensation compounds **15**, which could be isolated in 26% yield. However, the simple expedient of heating the crude reaction mixture with aqueous hydrochloric acid converted the byproduct to **14**, providing overall yields of 60-70% for ethyl orthoformate. The yields were lower (about 20%) with other orthoesters. Mono-alkylation of **10a** to give **10m** was easily achieved by deprotonation; overalkylation was prevented by the low nucleophilicity of the amino group

Scheme 3



caused by the electron-poor nature of the pyridine ring. Reduction and cyclization as above provided the *N*-methyl analog **14m** in good yield.

Compound **10a** was also easily converted to the hydroxy analog **16a** by diazotization and *in situ* hydrolysis; reduction and cyclization as before then provided the oxazolo[5,4-*b*]pyridine analog **18a**. Attempts were made to convert the intermediate **16a** to the mercaptopyridine **20a** (X = SH) *via* the chloropyridine **19a** (X = Cl) using standard methods, but in all cases only **16a** was recovered unchanged. We hypothesize that the strongly electron-withdrawing nature of the pyridine ring renders the intermediate chloropyridine extremely sensitive to hydrolysis, causing reversion to the starting material upon workup.

The examples provided demonstrate that this modification of the Guareschi synthesis is useful for preparing a variety of polysubstituted, highly functionalized pyridines, particularly with activated diketones. Further elaboration of the resulting nitroaminopyridines provides ready access to fused heterocyclic 5,6-pyridine ring systems.

EXPERIMENTAL

Reagents and solvents were obtained commercially unless otherwise indicated, and were used as received. Organic phases were dried over anhydrous magnesium sulfate, filtered and concentrated on a rotary evaporator at water aspirator pressure unless otherwise indicated. Chromatography was performed using the medium-pressure flash technique [29]. Melting points were obtained on a Thomas Hoover oil bath apparatus and are uncorrected. Proton nmr spectra were obtained at 300 MHz on a Varian Gemini 300 spectrometer, with tetramethylsilane as internal standard. Infrared spectra were obtained as potassium bromide pellets with a Perkin-Elmer 1710 FT spectrometer. Mass spectra were obtained with a Finnigan-MAT 8239 instrument, using chemical ionization with ammonia as reagent gas. Microanalyses were performed by Quantitative Technologies Incorporated, Bound Brook, New Jersey.

Nitroacetamidine (**8**).

Nitroacetonitrile was prepared according to a literature method [17]. Nitromethane (178 ml, 3.3 moles) was added dropwise with efficient stirring to a solution of sodium hydroxide (200 g, 5.0 moles) in water (400 ml) at room temperature. The temperature was maintained between 45° and 50° by adjusting the addition rate and ice cooling. The addition was complete after 35 minutes. After stirring for 15 minutes, the mixture was cooled to below 5°, and acidified with concentrated hydrochloric acid (approximately 420 ml) to pH 1.5. The nearly white solid was isolated by filtration and dissolved in ether while still wet. The organic phase was separated from the aqueous sludge, which was extracted with additional ether. The aqueous filtrate was also extracted with ether, and the combined extracts were dried, concentrated (below 20°) and dried further *in vacuo*. Methazonic acid was thus obtained as wet yellow-orange crystals (154.3 g, 89%); ¹H nmr (DMSO-*d*₆): δ 11.78 (s, 0.5H), 11.57 (s, 0.5H), 7.54 (t, 0.5H), 7.14 (t, 0.5H), 5.43 (d, 1H), 5.32

(d, 1H). A solution of the crude product (1.49 moles) in ether (780 ml) was heated to reflux, then treated with thionyl chloride (114 ml, 1.57 moles) at a rate which maintained gentle boiling. Addition was complete after 1.5 hours, and the mixture was kept at reflux for an additional hour. The mixture was cooled to room temperature, and the solution was decanted from a red sludge. The ether phase was washed with water, dried and concentrated. Nitroacetonitrile was obtained as a dark red liquid (120.5 g, 94%) which was about 85% pure (remainder mostly ether); ^1H nmr (DMSO- d_6): δ 6.14 (s).

Using a literature procedure [18], the crude nitroacetonitrile (about 1.2 moles) was dissolved in ether (400 ml) and cooled to -10° . Ethanol (70 ml, 1.19 moles) was added, and hydrogen chloride was bubbled through the mixture for 30 minutes while the temperature was kept below -5° . Stirring was continued for 2.5 hours while the bath was allowed to warm slowly to about 0° when a precipitate formed. After stirring on ice for 4.5 hours, the solid was isolated by filtration, rinsed with ether, and dried under nitrogen to provide ethyl nitroacetimidate hydrochloride as a tan-yellow solid (83.3 g, 42%). Ethanol (800 ml) was bubbled with anhydrous ammonia for 20 minutes at -20° . The crude imidate hydrochloride was added portionwise over 10 minutes to give a thick slurry. Stirring was continued for 10 minutes after addition was complete, and the mixture was filtered. The solid was washed with ethanol, and the filtrate was concentrated to provide ethyl nitroacetimidate as a light brown solid (62.7 g, 40%); ^1H nmr (DMSO- d_6): δ 9.25 (bs, 1H), 8.95 (bs, 1H), 6.60 (s, 1H), 4.15 (q, 2H), 1.25 (t, 3H).

Following a literature procedure [19], the crude imidate (0.47 mole) was combined with ethyl aminocrotonate (61 ml, 0.48 mole) and water (235 ml), and the mixture was heated at $65-70^\circ$ for 7 hours. After cooling to room temperature, the mixture was concentrated somewhat overnight under a nitrogen stream. Filtration provided a yellow solid, which was rinsed with a small amount of cold water and dried *in vacuo* to provide **8** as a yellow-tan solid (37.4 g, 77%) which was generally used without further purification; ^1H nmr (DMSO- d_6): δ 6.29 (s, 2H), 3.33 (bs, 2H), 2.39 (s, 1H); only a small amount (<10%) of the ketene aminal form was observed as a singlet at δ 6.43 and broad indistinct peaks at δ 7.6-7.2. Recrystallization from water gave a yellow solid, mp $199-206^\circ$ (lit [19] 209°).

Ethyl 3-(4-Phenylbenzoyl)-2-ketopropionate (**9a**).

This compound was prepared using a literature procedure [21]. Sodium hydride (60% in mineral oil, 5.64 g, 141 mmoles) was washed with hexane under nitrogen and suspended in benzene (240 ml). Ethanol (8.3 ml, 141 mmoles) was added dropwise at room temperature. When gas evolution subsided, the mixture was stirred for an additional 10 minutes, then cooled on ice. A solution of 4-acetylbiphenyl (18.50 g, 94.3 mmoles) and ethyl oxalate (15.4 g, 113 mmoles) in benzene (45 ml) was added over 80 minutes while keeping the temperature below 15° . The resulting thick yellow slurry was warmed to room temperature and stirred for 4.5 hours. Hydrochloric acid (1N, 200 ml) was added, and the mixture was extracted with ethyl acetate. The organic phase was dried and concentrated to provide a yellowish sticky solid, which was recrystallized from acetonitrile to give **9a** as a light yellow solid (19.60 g, 70%), mp $113-115^\circ$ (lit [30] 114° from ethanol); ^1H nmr (deuteriochloroform): δ 8.07 (d, 2H), 7.73 (d, 2H), 7.64 (d, 2H), 7.45 (m, 3H), 7.11 (s, 1H), 4.42 (q, 2H), 1.41 (t, 3H); ir: ν 1734 cm^{-1} ; ms: m/z 297 (100).

Ethyl 3-(4-(2-Fluorophenyl)phenyl)-2-ketobutyrate (**9b**).

A suspension of magnesium ethoxide (3.43 g, 30 mmoles) in toluene (50 ml) was treated at room temperature with a solution of 4-(2-fluorophenyl)propiophenone (4.57 g, 20 mmoles) and diethyl oxalate (4.07 ml, 30 mmoles) in toluene (100 ml) over 15 minutes. This was stirred at room temperature for 4 hours, then at reflux for 14 hours. Toluene and ethanol were then distilled from the mixture slowly over 60 minutes. After cooling to room temperature, 1N hydrochloric acid (100 ml) was added, the layers were separated, the aqueous phase was extracted further with dichloromethane, and the combined organic phases were dried and concentrated to give a yellow pasty material (6.75 g) which contained both starting materials, other products formed by retro-Claisen condensation, and the desired product (about 30% product by nmr integration). Attempted purification of the product led to decomposition, so this mixture was used directly in the next reaction; ^1H nmr (deuteriochloroform): δ 5.10 (q, 1H), 4.28 (q, 2H), 1.49 (d, 3H), 1.28 (t, 3H).

Ethyl 2-Amino-3-nitro-6-(4-biphenyl)pyridine-4-carboxylate (**10a**).

A mixture of **9a** (2.96 g, 10 mmoles) and **8** (1.24 g, 12 mmoles) in ethanol (50 ml) was heated at reflux for 16 hours. The mixture was cooled to room temperature and concentrated to give a yellow-brown solid, which was digested in toluene on a steam bath and filtered. The filtrate was concentrated to give a yellow solid. Chromatography (92:8 toluene/ethyl acetate) provided **10a** as a bright yellow solid (2.99 g, 83%), mp $156.5-157.5^\circ$ (ethanol); ^1H nmr (deuteriochloroform): δ 8.10 (d, 2H), 7.82 (d, 2H), 7.65 (d, 2H), 7.5-7.3 (3H), 7.22 (s, 1H), 6.82 (bs, 2H), 4.46 (q, 2H), 1.40 (t, 3H); ir: ν $3450, 3290, 1620\text{ cm}^{-1}$; ms: m/z 364 (100).

Anal. Calcd. for $\text{C}_{20}\text{H}_{17}\text{N}_3\text{O}_4$: C, 66.11; H, 4.72; N, 11.56. Found: C, 66.25; H, 4.62; N, 11.56.

Ethyl 2-Amino-3-nitro-6-(4-(2-fluorophenyl)phenyl)pyridine-4-carboxylate (**10b**).

The same procedure using crude **9b** provided **10b** as a bright yellow solid (1.46 g, 37%), mp $145.5-147^\circ$ (ethanol); ^1H nmr (deuteriochloroform): δ 7.67 (m, 2H), 7.57 (m, 2H), 7.48 (t, 1H), 7.35 (m, 1H), 7.21 (m, 2H), 6.75 (bs, 2H), 4.51 (q, 2H), 2.22 (s, 3H), 1.42 (t, 3H); ir: ν $3460, 1736\text{ cm}^{-1}$; ms: m/z 396 (100).

Anal. Calcd. for $\text{C}_{21}\text{H}_{18}\text{FN}_3\text{O}_4$: C, 63.79; H, 4.59; N, 10.63; F, 4.80. Found: C, 63.62; H, 4.50; N, 10.55; F, 4.82.

Ethyl 2-Amino-3-nitro-6-methylpyridine-4-carboxylate (**10c**).

A mixture of ethyl 2,4-dioxovalerate (1.58 g, 10 mmoles), **8** (1.03 g, 10 mmoles) and ethanol (50 ml) was heated at reflux for 45 minutes and cooled to room temperature. Concentration provided a yellow solid which was chromatographed (6:4 toluene/ethyl acetate) to give **10c** as a bright yellow solid (1.92 g, 85%), mp $104-106.5^\circ$ (hexane/ethyl acetate); ^1H nmr (deuteriochloroform): δ 6.73 (bs, 2H), 6.57 (s, 1H), 4.42 (q, 2H), 2.46 (s, 3H), 1.37 (t, 3H); ir: ν $3422, 1728\text{ cm}^{-1}$; ms: m/z 226 (100).

Anal. Calcd. for $\text{C}_9\text{H}_{11}\text{N}_3\text{O}_4$: C, 48.00; H, 4.92; N, 18.66. Found: C, 47.95; H, 4.72; N, 18.55.

2-Amino-3-nitro-4-trifluoromethyl-6-phenylpyridine (**10d**).

A mixture of trifluoroacetylacetophenone (2.16 g, 10 mmoles), **8** (1.03 g, 10 mmoles) and ethanol (50 ml) was heated at reflux for 72 hours and cooled to room temperature. Concentration provided a yellow solid, which was chromatographed

(96:4 toluene/ethyl acetate) to provide **10d** as a bright yellow solid (1.44 g, 51%), mp 116–119° (hexane/ethyl acetate); ^1H nmr (deuteriochloroform): δ 8.02 (m, 2H), 7.52 (m, 3H), 7.45 (s, 1H), 6.26 (bs, 2H); ms: m/z 284 (100).

Anal. Calcd. for $\text{C}_{12}\text{H}_8\text{F}_3\text{N}_3\text{O}_2$: C, 50.89; H, 2.85; N, 14.84; F, 20.12. Found: C, 50.91; H, 2.73; N, 14.77; F, 20.20.

2-Amino-3-nitro-4-trifluoromethyl-6-methylpyridine (**10e**).

A mixture of trifluoroacetylacetone (1.2 ml, 10 mmoles), **8** (1.03 g, 10 mmoles) and ethanol (50 ml) was heated at reflux for 23 hours and cooled to room temperature. Concentration provided an orange-yellow sticky solid, which was chromatographed (8:2 toluene/ethyl acetate) to provide **10e** as a bright yellow solid (769 mg, 35%), mp 169–171°; ^1H nmr (deuteriochloroform): δ 6.87 (s, 1H), 6.21 (bs, 2H), 2.52 (s, 3H); ms: m/z 222 (100).

Anal. Calcd. for $\text{C}_7\text{H}_6\text{F}_3\text{N}_3\text{O}_2$: C, 38.02; H, 2.73; N, 19.00; F, 25.77. Found: C, 37.99; H, 2.65; N, 18.89; F, 25.63.

2-Amino-3-nitro-4,6-dimethylpyridine (**10f**).

A mixture of acetylacetone (0.63 g, 6.37 mmoles), **8** (0.50 g, 4.90 mmoles) and ethanol (10 ml) was heated at reflux for 16 hours and cooled to room temperature. A precipitate formed which was collected by filtration and recrystallized (ethanol) to give **10f** as a bright yellow solid (550 mg, 69%), mp 168–170° (lit [14] 172–173° from methanol); ^1H nmr (deuteriochloroform): δ 6.41 (s, 1H), 6.30 (bs, 2H), 2.58 (s, 3H), 2.40 (s, 3H); ms: m/z 168 (100).

Anal. Calcd. for $\text{C}_7\text{H}_9\text{N}_3\text{O}_2$: C, 50.29; H, 5.43; N, 25.14. Found: C, 49.89; H, 5.14; N, 24.88.

2-Amino-3-nitro-6-phenylpyridine (**10g**).

A mixture of sodiobenzoylacetalddehyde [31] (1.25 g, 7.35 mmoles), ethereal hydrogen chloride (1*N*, 7.4 ml, 7.4 mmoles), **8** (0.50 g, 4.90 mmoles) and ethanol (10 ml) was heated at reflux for 16 hours, cooled to room temperature and poured into water. The resulting precipitate was collected by filtration, chromatographed (8:2 hexane/ethyl acetate) and recrystallized (hexane/ethyl acetate) to give **10g** as a bright yellow solid (750 mg, 60%), mp 150–152° (lit [15] 147–149° from ethanol/water); ^1H nmr (deuteriochloroform): δ 8.45 (d, 1H), 8.03 (m, 2H), 7.46 (m, 3H), 7.20 (d, 1H); ms: m/z 216 (100).

Anal. Calcd. for $\text{C}_{11}\text{H}_9\text{N}_3\text{O}_2$: C, 61.39; H, 4.22; N, 19.53. Found: C, 61.14; H, 4.25; N, 19.46.

2-Amino-3-nitro-4-methyl-6-phenylpyridine (**10h**).

A mixture of benzoylacetone (324 mg, 2.0 mmoles), **8** (206 mg, 2.0 mmoles) and ethanol (5 ml) was heated at reflux for 64 hours, cooled to room temperature and concentrated. The residue was chromatographed (9:1 hexane/ethyl acetate) to give **10h** as a bright yellow solid (153 mg, 33%), mp 124–126° (hexane/ethyl acetate; lit [14] 127–128° from methanol); ^1H nmr (deuteriochloroform): δ 7.98 (m, 2H), 7.47 (m, 3H), 7.02 (s, 1H), 6.92 (bs, 2H), 2.65 (s, 3H); ms: m/z 230 (100).

Anal. Calcd. for $\text{C}_{12}\text{H}_{11}\text{N}_3\text{O}_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.47; H, 4.71; N, 18.09.

When 0.5 equivalent of pyridinium acetate was included in the reaction mixture, **10h** was isolated (16%) along with 2-amino-3-nitro-4-phenyl-6-methylpyridine **11h** (43 mg, 9%), mp 165–170° (lit [14] 181–182° from methanol); ^1H nmr (deuteriochloroform): δ 7.42 (m, 3H), 7.27 (m, 2H), 6.52 (s, 1H), 6.06 (bs, 2H), 2.45 (s, 3H); ms: m/z 230 (100).

Anal. Calcd. for $\text{C}_{12}\text{H}_{11}\text{N}_3\text{O}_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.67; H, 4.78; N, 18.11.

When 0.5 equivalent of piperidinium acetate was included, none of the pyridine products were obtained, but 2-nitromethyl-4-methyl-6-phenylpyrimidine **12** was instead isolated as a pale yellow solid (160 mg, 35%), mp 56–57° (hexane/ethyl acetate); ^1H nmr (deuteriochloroform): δ 8.07 (m, 2H), 7.58 (s, 1H), 7.51 (m, 3H), 5.80 (s, 2H), 2.62 (s, 3H); ms: m/z 230 (100).

Anal. Calcd. for $\text{C}_{12}\text{H}_{11}\text{N}_3\text{O}_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.89; H, 4.76; N, 18.25.

Ethyl 2,3-Diamino-6-(4-biphenyl)pyridine-4-carboxylate (**13a**).

Compound **10a** (1.486 g, 4.09 mmoles) was hydrogenated in ethanol (70 ml) and tetrahydrofuran (70 ml) with 10% Pd on carbon (150 mg) at 60 psig for 22 hours at room temperature. The solution was filtered through celite, and the solid was washed with tetrahydrofuran. The filtrate was concentrated to provide **13a** as a yellow solid (1.52 g, ca. 100%). While this was generally used without further purification, it could be recrystallized (acetonitrile) to give a yellow-brown solid, mp 188–200° dec; ^1H nmr (deuteriochloroform): δ 7.98 (d, 2H), 7.72 (s, 1H), 7.65 (m, 4H), 7.45 (t, 2H), 7.35 (t, 1H), 5.47 (bs, 2H), 4.41 (q, 2H), 4.39 (bs, 2H), 1.43 (t, 3H); ir: ν 3456, 3424, 3338, 1680 cm^{-1} ; ms: m/z 334 (100).

Anal. Calcd. for $\text{C}_{20}\text{H}_{19}\text{N}_3\text{O}_2$: C, 72.05; H, 5.74; N, 12.60. Found: C, 71.86; H, 5.67; N, 12.55.

Ethyl 2,3-Diamino-6-(4-(2-fluorophenyl)phenyl)pyridine-4-carboxylate (**13b**).

Using the same method, **10b** (1.47 g, 3.72 mmoles) was reduced to the diamine (2.37 g) which was obtained as a gummy red material, very impure by nmr. It was used without further purification.

Ethyl 5-(4-Biphenyl)-3*H*-imidazo[4,5-*b*]pyridine-7-carboxylate (**14a**).

A mixture of crude **13a** (1.52 g, 4.09 mmoles) and triethyl orthoformate (30 ml) was heated at reflux for 6 hours, then concentrated. The residue was taken up in ethanol (20 ml) and 1*N* hydrochloric acid (40 ml) and heated at reflux for 60 minutes. The mixture was cooled on ice, and the solid which formed was collected by filtration, rinsed with ethanol and dried. This was chromatographed (92:8 chloroform/2-propanol) to provide **14a** as a tan powdery solid (1.00 g, 71% for 2 steps), mp >250°; ^1H nmr ($\text{DMSO}-d_6$): δ 8.65 (s, 1H), 8.25 (d + s, 3H), 7.84 (d, 2H), 7.77 (d, 2H), 7.52 (t, 2H), 7.41 (t, 1H), 4.52 (q, 2H), 3.32 (bs, 1H), 1.44 (t, 3H); ir: ν 3314, 1702 cm^{-1} ; ms: m/z 344 (100).

Anal. Calcd. for $\text{C}_{21}\text{H}_{17}\text{N}_3\text{O}_2$: C, 73.45; H, 4.99; N, 12.24. Found: C, 73.16; H, 4.92; N, 12.16.

If the acid treatment step was omitted, the bis-condensation product **15a** could also be isolated (26%), mp 224–226° (acetone); ^1H nmr ($\text{DMSO}-d_6$): δ 9.18 (s, 2H), 8.53 (s, 1H), 8.29 (s, 2H), 8.24 (d, 4H), 7.67 (d, 8H), 7.42 (m, 6H), 4.43 (q, 4H), 4.05 (q, 2H), 1.36 (t, 9H); ir: ν 1720 cm^{-1} ; ms: m/z 743 (100); hrms: Calcd. 743.2982. Found 743.2973.

Anal. Calcd. for $\text{C}_{45}\text{H}_{38}\text{N}_6\text{O}_5$: C, 72.66; H, 5.28; N, 11.30. Found: C, 71.50; H, 4.94; N, 10.99.

Ethyl 5-(4-(2-Fluorophenyl)phenyl)-6-methyl-3*H*-imidazo[4,5-*b*]pyridine-7-carboxylate (**14b**).

Using the same procedure, crude **13b** was converted to **14b**

(970 mg, 63% for two steps) as a pale pinkish solid, mp 201–202.5° (acetonitrile), which appeared to be a mixture of two tautomers by nmr; ¹H nmr (deuteriochloroform): δ 13.64 (bs, 0.5H), 10.33 (bs, 0.5H), 8.34 (s, 0.5H), 7.77 (s, 0.5H), 7.75–7.1 (8H), 4.59 (q, 1H), 4.56 (q, 1H), 2.75 (s, 1.5H), 2.53 (s, 1.5H), 1.51 (t, 1.5H), 1.47 (t, 1.5H); ir: ν 3000 (broad), 1710 cm⁻¹; ms: m/z 376 (100).

Anal. Calcd. for C₂₂H₁₈FN₃O₂: C, 70.39; H, 4.83; N, 11.19; F, 5.06. Found: C, 70.07; H, 4.81; N, 11.24; F, 4.95.

Ethyl 2-Methyl-5-(4-biphenyl)-3H-imidazo[4,5-*b*]pyridine-7-carboxylate (**14k**).

Using the same procedure, **13a** was condensed with triethyl orthoacetate to provide, after chromatography (9:1 chloroform/2-propanol), **14k** as a tan solid (20%), mp 234–236.5° (acetonitrile); ¹H nmr (deuteriochloroform): δ 9.96 (bs, 1H), 8.26 (d, 2H), 8.18 (s, 1H), 7.73 (d, 2H), 7.68 (d, 2H), 7.47 (t, 2H), 7.37 (t, 1H), 4.55 (q, 2H), 2.75 (s, 3H), 1.50 (t, 3H); ir: ν 1714 cm⁻¹; ms: m/z 358 (100).

Anal. Calcd. for C₂₂H₁₉N₃O₂: C, 73.93; H, 5.36; N, 11.76. Found: C, 73.64; H, 5.12; N, 11.75.

Ethyl 2-Phenyl-5-(4-biphenyl)-1H-imidazo[4,5-*b*]pyridine-7-carboxylate (**14l**).

Using the same procedure, **13a** was condensed with triethyl orthobenzoate at 150°. Chromatography (8:2 toluene/ethyl acetate) provided **14l** as a tan solid (27%), mp 211–213° (acetonitrile); ¹H nmr (deuteriochloroform): δ 10.43 (bs, 1H), 8.32 (d, 2H), 8.25 (s, 1H), 8.22 (m, 2H), 7.75 (d, 2H), 7.69 (d, 2H), 7.58 (m, 3H), 7.48 (t, 2H), 7.38 (t, 1H), 4.58 (q, 2H), 1.55 (t, 3H); ir: ν 3442, 3260, 1710 cm⁻¹; ms: m/z 420 (100).

Anal. Calcd. for C₂₇H₂₁N₃O₂: C, 77.31; H, 5.05; N, 10.02. Found: C, 76.95; H, 5.00; N, 10.09.

Ethyl 2-Methylamino-3-nitro-6-(4-biphenyl)pyridine-4-carboxylate (**10m**).

Sodium hydride (60% in mineral oil, 100 mg, 2.5 mmoles) was washed with hexane and suspended in tetrahydrofuran (5 ml). A solution of **10a** (727 mg, 2.0 mmoles) and iodomethane (0.25 ml, 4.0 mmoles) in tetrahydrofuran (15 ml) was added over 10 minutes at 0° with gas evolution. The red solution was stirred at room temperature for 19 hours, when tlc showed starting material remaining. Additional sodium hydride (20 mg) and iodomethane (8 drops) were added and the mixture was stirred overnight. After 44 hours total, the mixture was poured into 1N hydrochloric acid (40 ml) and extracted with methylene chloride. The organic phase was dried and concentrated to yield an orange solid, which was recrystallized from ethanol to provide **10m** as orange crystals (519 mg, 68%), mp 171–174°, ¹H nmr (deuteriochloroform): δ 8.33 (bq, 1H), 8.18 (d, 2H), 7.73 (d, 2H), 7.66 (d, 2H), 7.49 (t, 2H), 7.40 (t, 1H), 7.13 (s, 1H), 4.46 (q, 2H), 3.31 (d, 3H), 1.41 (t, 3H); ir: ν 3382, 1742 cm⁻¹; ms: m/z 378 (100%).

Anal. Calcd. for C₂₁H₁₉N₃O₄: C, 66.83; H, 5.07; N, 11.13. Found: C, 66.41; H, 4.92; N, 10.85.

Ethyl 3-Methyl-5-(4-biphenyl)-3H-imidazo[4,5-*b*]pyridine-7-carboxylate (**14m**).

A mixture of **10m** (1.55 g, 4.10 mmoles), 10% palladium on carbon (155 mg), ethanol (70 ml) and tetrahydrofuran (70 ml) was hydrogenated at 50 psig at room temperature for 22 hours. The mixture was filtered through celite, and the catalyst was

rinsed with ethyl acetate. The filtrate was concentrated to provide **13m** as a yellowish glassy solid, which was used without further purification; ¹H nmr (deuteriochloroform): δ 8.10 (d, 2H), 7.66 (m, 5H), 7.46 (t, 2H), 7.34 (t, 1H), 5.42 (bs, 2H), 4.41 (q, 2H), 3.15 (s, 3H), 1.44 (t, 3H). This material was combined with triethyl orthoformate (30 ml) and heated at reflux for 5 hours. The mixture was concentrated to provide a tan solid, which was chromatographed (95:5 chloroform/2-propanol) to give **14m** as a pale tan solid (1.139 g, 78%), mp 154.6–156.2°, ¹H nmr (deuteriochloroform): δ 8.34 (s, 1H), 8.24 (d, 2H), 8.21 (s, 1H), 7.76 (d, 2H), 7.68 (d, 2H), 7.49 (t, 2H), 7.18 (t, 1H), 4.61 (q, 2H), 4.02 (s, 3H), 1.51 (t, 3H); ir: ν 1712 cm⁻¹; ms: m/z 358 (100).

Anal. Calcd. for C₂₂H₁₉N₃O₂: C, 73.93; H, 5.36; N, 11.76. Found: C, 73.56; H, 5.30; N, 11.60.

Ethyl 1-Hydroxy-2-nitro-6-(4-biphenyl)pyridine-4-carboxylate (**16a**).

A suspension of **10a** (182 mg, 0.50 mmole) in trifluoroacetic acid (10 ml) and water (4 ml) was stirred on ice and treated with a solution of sodium nitrite (69 mg, 1.00 mmole) in water (1 ml). The mixture formed a red-brown solution, then a yellow slurry after 2 hours at room temperature. It was poured into water (125 ml), stirred briefly, and filtered. The solid was washed with water and dried to provide **16a** as a bright yellow solid (175 mg, 100%), mp >250° (acetonitrile); ¹H nmr (deuteriochloroform): δ 13.0 (b, 1H), 7.93 (d, 2H), 7.80 (d, 2H), 7.67 (d, 2H), 7.49 (t, 2H), 7.44 (m, 1H), 7.00 (s, 1H), 4.43 (q, 2H), 1.38 (t, 3H); ir: ν 2950, 1734 cm⁻¹; ms: m/z 365 (4), 335 (100).

Anal. Calcd. for C₂₀H₁₆N₂O₅: C, 65.93; H, 4.43; N, 7.69. Found: C, 65.69; H, 4.39; N, 7.65.

Ethyl 5-(4-Biphenyl)oxazolo[5,4-*b*]pyridine-7-carboxylate (**18a**).

A mixture of **16a** (800 mg, 2.20 mmoles), 10% palladium on charcoal (80 mg), ethanol (50 ml) and tetrahydrofuran (50 ml) was hydrogenated at room temperature under 50 psig for 22 hours. The mixture was filtered through celite, and the catalyst was washed with tetrahydrofuran. The filtrate was concentrated to provide **17a** as a yellow powder (777 mg) which was used without further purification; ¹H nmr (deuteriochloroform): δ 10.2 (b, 1H), 7.7–7.6 (6H), 7.47 (t, 2H), 7.38 (t, 1H), 6.98 (s, 1H), 6.70 (bs, 2H), 4.39 (q, 2H), 1.41 (t, 3H); ms: m/z 335 (100). The crude product was mixed with triethyl orthoformate (30 ml) and heated at reflux for 4 hours, then cooled and concentrated *in vacuo*. The resulting brown solid was chromatographed (8:2 toluene/ethyl acetate) to provide **18a** as a light yellow solid (589 mg, 78%), mp 161–163° (acetonitrile); ¹H nmr (deuteriochloroform): δ 8.43 (s, 1H), 8.36 (s, 1H), 8.22 (d, 2H), 7.76 (d, 2H), 7.67 (d, 2H), 7.48 (t, 2H), 7.19 (t, 1H), 4.61 (q, 2H), 1.52 (t, 3H); ir: ν 1718 cm⁻¹; ms: m/z 345 (100).

Anal. Calcd. for C₂₁H₁₆N₂O₃: C, 73.24; H, 4.68; N, 8.13. Found: C, 72.95; H, 4.66; N, 8.28.

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