A General Synthesis of 5-Arylnicotinates

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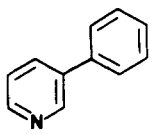
Arylboronic acids have been found to couple efficiently with 5-bromonicotinates to yield 5-arylnicotinates. The reaction is considerably more sensitive to steric inhibition in the arylboronic acid component than in the pyridyl bromide 4. The dianion salt of the boronic acid is implicated as the reactive intermediate responsible for the facile coupling reaction. Pure arylboronic acids are best prepared by using triisopropyl borate as the transmetalating agent.

In contrast to the numerous synthetic methods available for 2- and 4-arylpyridines,[1] methodology for the 3-arylpyridines is scarce.[2] The parent member of this interesting class of compounds, 3-phenylpyridine (1), has been reported to possess antimicrobial activity[3] and is an aroma constituent of roasted cocoa and tea.[4] As a result of the potent biological activity of nicotinic acid and its various acyl derivatives, we became interested in the 5-arylnicotinates 2.[5] The introduction of a 5-phenyl substituent in a nicotinate-based vasodilator caused a marked decrease in heart rate associated with increased peripheral vasodilatation.[6a,b] The 5-phenylnicotinate bearing a meta-amino substituent (3) was sought in particular as a key intermediate in a new synthetic strategy for lysergic acid.[6c]



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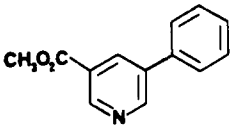

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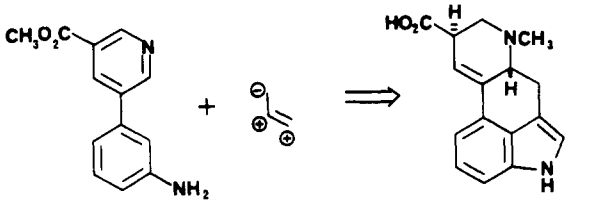
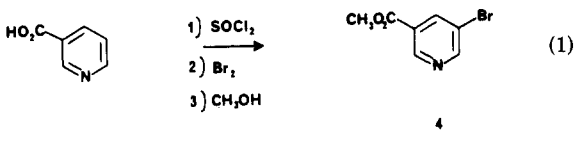


3 lysergic acid

While the 5-(3-aminophenyl)nicotinate 3 was unknown, the simpler descarboxy precursor 3-(3-nitrophenyl)pyridine had been prepared in poor yield (9%) together with the two other possible regioisomers (29% α and 4.5% γ) by the S_EAr type reaction of 3-nitrobenzenediazonium chloride with pyridine.[7]

The 5-bromonicotinates were chosen as convenient starting materials for the introduction of the 5-aryl substituents, since they are readily available from nicotinic acid by bromination of nicotinoyl chloride hydrochloride[8] and esterification (87% overall for methyl 5-bromonicotinate from nicotinic acid).

The most convergent approach to the synthesis of the (3-aminophenyl)nicotinate 3 is the coupling of an organometallic synthetic equivalent of the 3-aminophenyl carbanion 5 with the 5-bromonicotinate 4. Since there are a variety of methods available for the conversion of an arylnitro group to an aniline, the 5-(3-nitrophenyl)-



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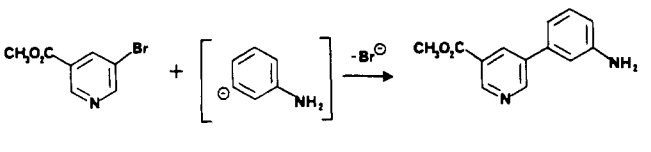
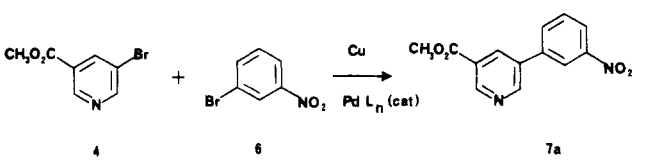


4 5 3

(2)

nicotinate 7a was chosen as a convenient precursor. Thus, the method of coupling would have to tolerate the presence of both an ester and nitro functionalities.



4 6 7a

(3)

The Ullman biaryl synthesis has been used successfully for the preparation of nitro and ester containing biaryls, although for the unsymmetrical biaryls a large excess of one of the two components is usually required.[9] Due to inherent differences in the reduction potential of the two

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Table I. Ullman Reaction of Bromides 4 and 6[a]

4, mmol	6, mmol	Cu bronze, mmol	cat.[b]	% yield of 7a
1	1	2	none	0
1	1	2	$Pd(PPh_3)_4$	20
1	2	4	$Pd(PPh_3)_4$	32
1	2	4	$Pd(P(o\text{-tol})_3)_2$[d]	0
1	4	8	$Pd(P(o\text{-tol})_3)_2$[d]	40
1	1	0	$Pd(P(o\text{-tol})_3)_2$[d,e]	0

[a] All reactions were carried out at reflux in DMF solvent, 0.5 M in 4. [b] 3 mol % catalyst was used in all reactions. [c] Yields refer to purified product. [d] This catalyst was formed in situ from palladium acetate, 2 equiv of tri-o-tolylphosphine, and 2 equiv of triethylamine. [e] This reaction was carried out in the absence of copper but with 1 mmol of triethylamine.

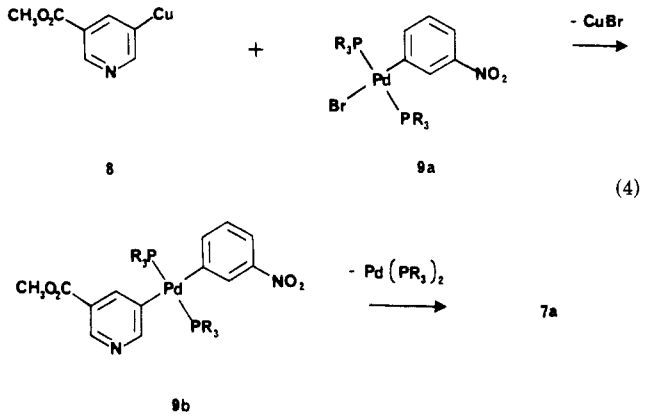
aryl halides in this case (4 and 6), we reasoned that the method might be adaptable by employment of an appropriate transition-metal catalyst.[10] Phenylzinc chloride and phenylboronic acid have recently been reported to undergo coupling with aryl bromides in the presence of low-valent nickel and palladium complexes.[11,12]

Results and Discussion

When the bromides 4 and 6 were allowed to react in refluxing *N,N*-dimethylformamide (DMF) for 8 h in the presence of excess copper bronze, none of the arylnicotinate **7a** or bromonicotinate 4 could be detected. The isolated reaction product consisted of methyl nicotinate (86%), 3-bromonitrobenzene (**6**, 97%), and 3,3′-dinitrobiphenyl (3%). If the reaction was instead carried out with addition of a catalytic quantity of tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$),[13] the desired product **7a** was isolated in 20% yield. Improvements in the yield were obtained by using an excess of the 3-bromonitrobenzene (**6**) and the more stable bis(tri-o-tolylphosphine)palladium(0) complex ($Pd(P(o\text{-tol})_3)_2$),[14] generated in situ from triethylamine, palladium acetate, and tri-o-tolylphosphine as catalyst.[15] In the absence of copper, the reaction failed to produce any of the coupled product **7a**.

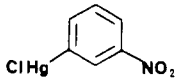
A possible mechanism consistent with these results might be as follows. Since the bromonicotinate 4 reacts faster than the 3-bromonitrobenzene (**6**) with copper bronze, the palladium catalyst may react with the bromide **6** to form the arylpalladium bromide **9a** (eq 4). Reaction of the postulated pyridylcopper(I) species 8 with arylpalladium bromide **9a** would lead to an arylpyridylpalladium(II) complex **9b**. The 1,1-reductive elimination from diarylpalladium intermediates has been well established as a favorable mode of decomposition.[16]

In view of the only moderate success of the palladium-catalyzed Ullman synthesis of the desired arylnicotinate **7a**, other organometallic equivalents of the carbanion **5** were investigated. Since the preparation of arylzinc reagents requires the intermediacy of an organomagnesium



or -lithium reagents[17] and both are incompatible with the nitro functionality, the isoelectronic arylmercuric chlorides were examined. While there were no reports of coupling of aryl- or vinylmercurials with aryl halides, the transmetalation with low-valent palladium, nickel, and rhodium complexes had been observed.[18]

Unfortunately, neither the readily available (3-nitrophenyl)mercuric chloride[19] (**10**) nor phenylmercuric chloride would couple with the bromonicotinate 4 under any of the conditions we tried (DMF or hexamethylphosphoramide (HMPA) at 150 °C with either 5 mol % $Pd(PPh_3)_4$, $Pd(P(o\text{-tol})_3)_2OAc_2{\cdot}Et_3N$, or $RhCl(PPh_3)_3$ and tetrahydrofuran (THF) at 25 °C with 5 mol % $NiCl_2(PPh_3)_2((i\text{-}Bu)_2AlH)$. Attempts to induce transmetalation of these arylmercuric chlorides to the more reactive arylzinc reagent with zinc dust or di-*n*-butylzinc in THF or DMF also failed.[20] The coupling of phenylzinc chloride with bromonicotinate 4 was successful for the preparation of 5-phenylnicotinate **13a** (86%), demonstrating the greater reactivity of the arylzinc reagents over the arylmercurials.



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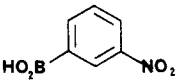

11a

The ease of preparation of (3-nitrophenyl)boronic acid[21] prompted us to investigate its potential as a convenient synthon for the carbanion **5**. We were rewarded to find that when equimolar quantities of the methyl 5-bromonicotinate (4) and (3-nitrophenyl)boronic acid (**11a**) were allowed to react under reflux (benzene and aqueous 2 M Na_2CO_3) for 6 h in the presence of 3 mol % of $Pd(PPh_3)_4$ (method A), the desired methyl 5-(3-nitrophenyl)nicotinate was isolated in 80% yield. While these same conditions[12] were found to work equally for the phenylboronic acids

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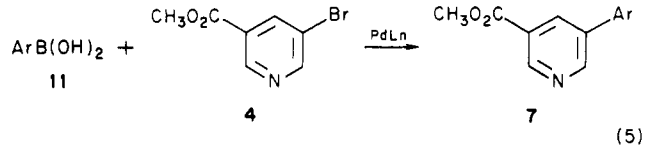
(24) Rogues, B. P.; Florentin, D.; Callanquin, M. *J. Heterocycl. Chem.* **1975**, *12*, 195–6.

Table II. Preparation of Methyl 5-Arylnicotinates (7)



(5)

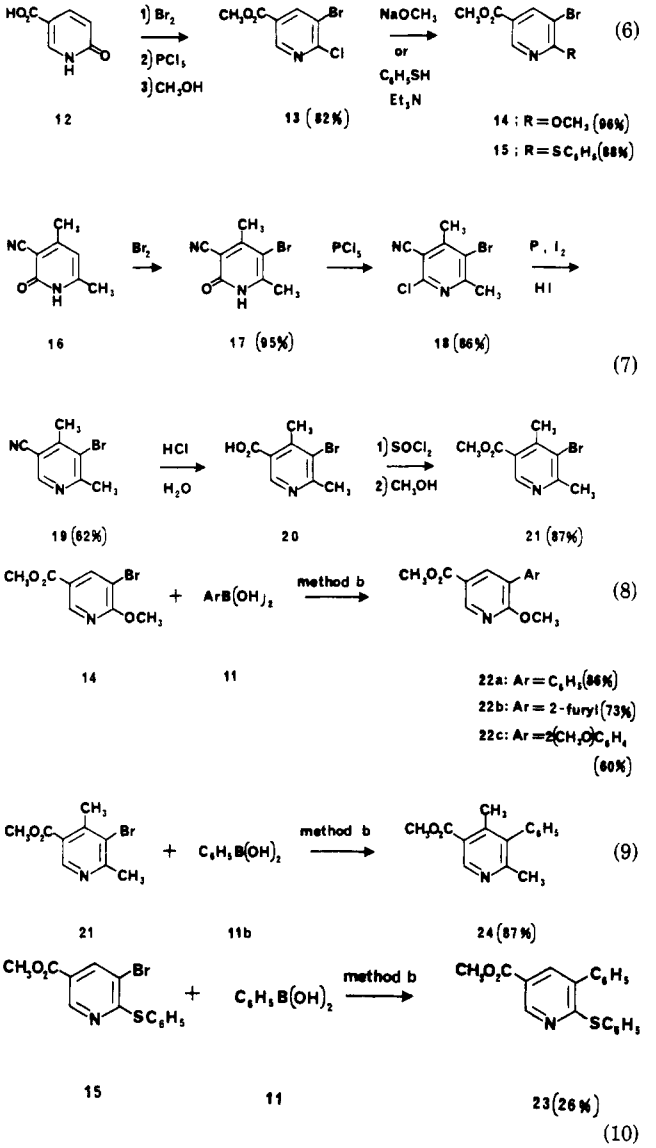
entry	boronic acid, Ar	catalyst	method[b]	% yield[c] of 7
a	3-$(NO_2)C_6H_4$	A	A (B)	80 (92)[d]
b	C_6H_5	A	A (B)	86 (98)[d]
c	3-$(CH_3)C_6H_4$[21]	A	A (B)	88 (98)[d]
d	2-$(CH_3)C_6H_4$[22]	B	A (B)	12 (81)[d]
e	2-$(NO_2)C_6H_4$[21]	B	A (B)	6 (61)[d]
f	2-$(CH_3O)C_6H_4$[22]	B	B	70
g	2,4,6-$(CH_3)C_6H_2$[23]	A or B	B	0
h	2-furyl[24]	B	B	86
i	3-furyl[24]	B	B	83

[a] catalyst A = $(Pd(PPh_3)_4$; catalyst B = $Pd(OAc)_2$ and $(P(o\text{-}tol)_3)_2$·Et_3N. [b] Method A, benzene–2 M Na_2CO_3, reflux 6 h; method B, DMF–Et_3N, 100 °C, 2–3 h. [c] Yields of isolated purified products. [d] Yields in brackets were obtained by using method B.

with meta or para substituents (**11a–c**), the ortho-substituted boronic acids **11d–f** reacted only slowly (incomplete after 3 days) and gave much lower yields of coupled products **7d–f**. For these cases an alternative procedure was developed (method B: DMF solvent at 100 °C with 2 mol % palladium catalyst and 1 equiv of Et_3N). Under these nonaqueous conditions, the coupling reaction of 5-bromonicotinate **4** with arylboronic acis **11a–f** was complete after 2 h with isolated yields of the 5-arylnicotinates **7a–f** ranging from 75 to 97% (Table II). This nonaqueous procedure was also found to be more useful for the coupling of the heterocyclic furanboronic acids **11h** and **11i**. Neither of these procedures was successful for effecting the coupling of the more sterically hindered 2,4,6-trimethyl boronic acid **11f** with the bromonicotinate **4**. Only traces of the desired product could be detected after 2 weeks at 100 °C (method B). This coupling method seems to therefore be limited to arylboronic acids with only one ortho substituent.

In order to further define the scope and limitations of the coupling reaction (eq 6), the novel 5-bromonicotinates **14**, **15**, and **21** were synthesized as shown below (eq 7 and 8). The ortho-substituted 6-methoxy- and 6-(phenylthio)-5-bromonicotinates **14** and **15** underwent smooth coupling with a variety of aryl- and heteroarylboronic acids including the more sterically crowded (2-methoxyphenyl)boronic acid **11f**.[25] In contrast to the unreactive nature observed for the (2,4,6-trimethylphenyl)boronic acid (**11g**), and 4,6-dimethyl-5-bromonicotinate **21** afforded an 87% yield of 4,6-dimethyl-5-phenylnicotinate **24** upon reaction under the usual conditions (method B) with phenylboronic acid. These results indicate a greater sensitivity to steric hindrance in the arylboronic acid component than in the aryl bromide. Consistent with this rationale, neither of the ortho-substituted boronic acid **11d** or **11g** would undergo the coupling reaction with the more sterically congested 4,6-dimethyl-5-bromonicotinate **21**.

An examination of the substitution on the boron atom revealed another important aspect of the coupling reaction. Neither diphenylboronic acid[28] (**25**) or triphenylboron[29]



(6)

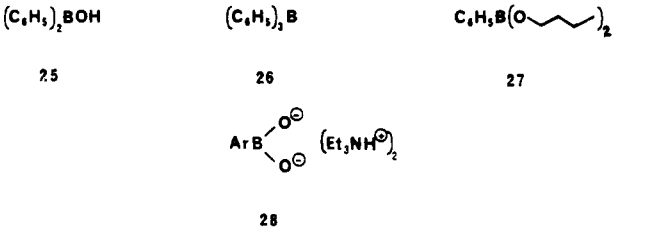
(7)

(8)

(9)

(10)

(**26**) would couple under these reaction conditions (method A or B) with the bromonicotinate **4**. In addition, the di-*n*-butyl boronate **27**[30] would not enter into the coupling reaction under the nonaqueous conditions (method B). These results suggest that the arylboronate dianion **28** is the reactive organometallic intermediate which attacks the arylpalladium bromide complex **10** to produce the penultimate diarylpalladium(II) complex during the course of the reaction. It also becomes clear that the arylboronic acid component should be free of di- and triarylboron species for best results. While these impurities were often



found to be present in the products of reaction of arylmagnesium and -lithium reagents with the commonly used trimethyl- or tributylborate esters,[31,32] by using **2** and **5**

(25) Neither and 6-chloro-5-bromonicotinate **13** nor 3-carbomethoxy-5-bromo-2(1*H*)-pyridone would couple with phenylboronic acid under the conditions described herein.

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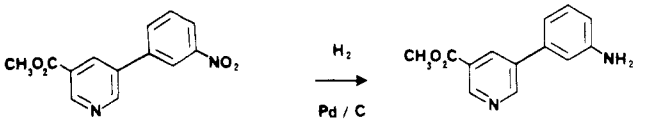
equiv of triisopropylborate at low temperatures (−78 °C), we were able to obtain consistently high yields of pure arylboronic acids.

Finally, conversion of the 5-(3-nitrophenyl)nicotinate **7a** into the desired 5-(3-aminophenyl)nicotinate **3** was effected by catalytic hydrogenation over 5% palladium on carbon catalyst in 96% isolated yield. The neurological activity (CNS) of these arylnicotinates and their utility in the total synthesis of lysergic acid is currently under investigation.



7a 3 (96%)

(11)

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by MicAnal Organic Microanalysis of Tucson, AZ. Ultraviolet absorption measurements were made on a Hewlett-Packard 8450A diode array spectrophotometer. Infrared spectra were recorded on either a Perkin-Elmer 710B or Beckman IR-12 spectrophotometer. Proton magnetic resonance spectra were recorded on either a Varian T-60 (60-MHz) or a Bruker WP-200 (200-MHz) spectrometer. High-resolution mass spectra (HMRS) were obtained on an AEI Kratos MS902 mass spectrometer. Thin-layer chromatography (TLC) was performed by using E. Merck silica gel 60F-254 (0.25-mm) analytical glass plates. Development of the TLC plates was effected with either ultraviolet absorption (UV) iodine vapor or a 10% ethanolic solution of phosphomolybdic acid (with heating to 110 °C). E. Merck silica gel 60 (230-400 mesh) was used for flash chromatography.[36]

Tetrahydrofuran (THF) was distilled from sodium benzophenone. Mallinckrodt "reagent grade" dimethylformamide (DMF) was used after a minimum of 4 days storage over 4-Å molecular sieves that had been dried by heating in a microwave oven for 5–10 min and then placed under vacuum (0.05 mm) in a desiccator for 30 min. Triethylamine was freshly distilled from P_2O_5 under a nitrogen atmosphere. Thionyl chloride (Aldrich, 97%) was distilled under nitrogen from linseed oil. Palladium acetate, tri-*o*-tolylphosphine, and 5% palladium on carbon were purchased from Spex Industries, Inc. Copper bronze powder was the "Cres-Lite extra small" grade purchased from Crescent Bronze Powder Co. Inc., Los Angeles, CA 90015. Tetrakis(triphenylphosphine)palladium(0) was prepared as described by Coulson[13] and was stored in the dark under a dry nitrogen atmosphere. All other reagents and solvents were reagent grade and were used without further purification.

Evaporative distillation was performed bulb to bulb by using a Büchi Glass microdistillation oven Model GKR-50. "Removal of excess reagents or solvents under reduced pressure" refers to either a short-path distillation into a dry ice/acetone cooled receiver flask or concentration on a Büchi Model R-110 rotary evaporator equipped with a heated bath ($T < 70$ °C).

Methyl 5-Bromonicotinate (4). A stirred mixture of nicotinic acid (100 g, 0.8 mol) and thionyl chloride (235 mL, 3.2 mol) was heated to reflux under a $CaCl_2$ drying tube for 24 h. The excess $SOCl_2$ was removed by distillation under reduced pressure, and the resulting crystalline solid was heated with 130 g (0.8 mol) of bromine to 150 °C (oil bath temperature) for 1 h.[8a] After being cooled to 25 °C overnite, the reaction flask was cooled in an ice bath and a mixture of 200 mL of MeOH and 300 mL of CH_2Cl_2 was added slowly. The resulting mixture was heated to reflux for 30 min, then cooled, and partitioned between 2 N NaOH (400 mL) and CH_2Cl_2 (800 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to dryness. Purification of the crude product (175 g) by recrystallization from aqueous methanol afforded 148 g (85%) of pure methyl 5-bromonicotinate (**4**):[8b] mp 98–99 °C (MeOH); TLC R_f 0.40 (30% EtOAc/hexane); IR ($CHCl_3$) 3000, 2960, 1735 (C=O), 1580, 1560, 1450, 1435, 1420, 1315, 1280, 1220, 1170, 1120, 1025, 970, 910, 850, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.95 (s, 3 H), 8.4 (t, 1 H, J = 2 Hz), 8.9 (d, 1 H, J = 2 Hz), 9.15 (d, 1 H, J = 2 Hz).

General Procedure for Coupling the Bromides 4 and 6 in the Presence of Copper Bronze. A stirred mixture of methyl 5-bromonicotinate (**4**, 0.217 g, 1 mmol), 3-bromonitrobenzene (**6**, 0.202 g, 1 mmol), copper bronze powder (2–8 mmol), and 0.03 mmol of a palladium catalyst (catalyst A, $Pd(PPh_3)_4$; catalyst B, palladium acetate (7 mg, 0.03 mmol), tri-*o*-tolylphosphine (18 mg, 0.06 mol), and 0.01 mL of Et_3N (0.07 mmol)) in 3 mL of dry DMF was heated under a nitrogen atmosphere to 180 °C for 8 h. After being cooled to 25 °C, the reaction was diluted with 50 mL of CH_2Cl_2, filtered, and washed twice with 10 mL of 10% aqueous NH_3. The organic layer was dried ($MgSO_4$) and then concentrated under reduced pressure. Purification by flash chromatography[36] using 30% EtOAc in hexane afforded the pure products.

Methyl 5-(3-Nitrophenyl)nicotinate (7a). From 2.2 g of bromonicotinate **4** (10 mmol), 8 g of 3-bromonitrobenzene (40 mmol), 5 g (80 mmol) of copper bronze powder, and 0.3 mmol of catalyst B using the general procedure described above, there was obtained 1.05 g (40%) of a white solid product: mp 179–180 °C (Et_2O/CH_2Cl_2); IR ($CHCl_3$) 3000, 1720 (C=O), 1520, 1430, 1340, 1320, 1245, 1220, 1105, 1050, 1020, 980, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.0 (s, 3 H), 7.5–8.4 (m, 4 H), 8.7 (dd, 1 H, J = 2, 2.5 Hz), 9.3 (d, 1 H, J = 2.5 Hz), 9.5 (d, 1 H, J = 2.0 Hz). Anal. Calcd for $C_{13}H_{10}N_2O_4$: C, 60.47; H, 3.90; H, 10.85. Found: C, 60.21; H, 3.62; N, 10.57.

General Procedure for the Palladium-Catalyzed Coupling of Arylboronic Acids with 5-Bromonicotinates. Method A. The procedure described by Miyaura, Yanagi, and Suzuki[12] was modified in the following manner. To a stirred solution of the methyl 5-bromonicotinate (10 mmol) and $Ph(PPh_3)_4$ (0.3 mmol) in 20 mL of toluene under a nitrogen atmosphere was added 10 mL of a 2 M aqueous solution of Na_2CO_3 and 12 mmol of the arylboronic acid in 5 mL of MeOH. The vigorously stirred mixture was warmed to 80 °C for 6 h, then cooled, and partitioned between CH_2Cl_2 (100 mL) and 2 M aqueous Na_2CO_3 (50 mL) containing 5 mL of concentrated NH_3. The organic layer was dried ($MgSO_4$), and then concentrated to dryness under reduced pressure. Evaporative distillation and/or flash chromatography[36] on silica gel afforded the pure methyl 5-arylnicotinates.

Method B. A stirred mixture of 10 mmol of the methyl 5-bromonicotinate, 15 mmol of the arylboronic acid, 4.2 mL (30 mmol) of Et_3N, 0.067 g (0.3 mmol) of $Pd(OAc)_2$, and either 0.19 g (0.62 mmol) of tri-*o*-tolylphosphine (catalyst A) or 0.16 g (0.62 mmol) of PPh_3 (catalyst B) in 40 mL of DMF was heated under a nitrogen atmosphere to 100 °C for 2–3 h. The solvents were distilled off under reduced pressure, and the residue was partitioned between CH_2Cl_2 (100 mL) and 10% aqueous NH_3. The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by evaporative distillation and/or flash chromatography[36] on silica gel afforded the pure methyl 5-arylnicotinates.

Methyl 5-(3-Nitrophenyl)nicotinate (7a). From 21.7 g (100 mmol) of methyl 5-bromonicotinate (**4**), 3.5 g (3 mmol) of $Ph(PPh_3)_4$, 20 g (100 mmol) of (3-nitrophenyl)boronic acid (**11a**), 200 mL of toluene, 100 mL of 2 M aqueous Na_2CO_3, and 50 mL of MeOH, method A gave 20.8 g (80%) of a white solid.

From 21.7 g (100 mmol) of methyl 5-bromonicotinate (**4**), 25 g (150 mmol) of (3-nitrophenyl)boronic acid (**11a**), 42 mL of Et_3N, 0.67 g (3 mmol) of $Pd(OAc)_2$, 1.9 g (6.2 mmol) of tri-*o*-tolylphosphine, and 40 mL of DMF, method B gave 24 g (92%) of white solid: mp 179–180 °C (Et_2O/CH_2Cl_2); TLC R_f 0.30 (10% EtOAc/CH_2Cl_2); all other spectral characteristics were identical with those obtained above for the copper-mediated coupling of 3-bromonitrobenzene and methyl 5-bromonicotinate (**4**).

Methyl 5-Phenylnicotinate (7b). From methyl 5-bromonicotinate (**4**) and phenylboronic acid, method A gave 1.83 g (86%)

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and method B gave 2.1 g (98%) of white crystals: mp 44.5–50 °C (hexane); TLC R_f 0.35 (30% EtOAc/hexane); IR ($CHCl_3$) 3000, 2950, 1735, 1600, 1560, 1500, 1460, 1440, 1420, 1310, 1260, 1210, 1160, 1110, 1060, 1020, 1000, 960, 900, 860, 700, 660 cm^{-1}; ^1H NMR (CCl_4) δ 4.0 (s, 3 H), 7.4–7.8 (m, 5 H), 8.5 (t, 1 H, J = 2.5 Hz), 9.0 (d, 1 H, J = 2.5 Hz), 9.2 (d, 1 H, J = 2.5 Hz). Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.23; H, 5.20; N, 6.57. Found: C, 73.18 H, 5.14; N, 6.47.

Methyl 5-(3-Methylphenyl)nicotinate (7c). From methyl 5-bromonicotinate (4) and (3-methylphenyl)boronic acid (**11c**),[21] method A gave 2.0 g (86%) and method B gave 2.2 g (98%) of a white solid: mp 55–56.5 °C (hexane); TLC R_f 0.4 (30% EtOAc/hexane); IR ($CHCl_3$) 3100, 1720, 1580, 1440, 1310, 1260, 1200, 1160, 1110, 1060, 1020, 980, 960, 900, 880, 810, 700 cm^{-1}; ^1H NMR (CCl_4) δ 2.5 (s, 3 H), 4.0 (s, 3 H), 7.3–7.6 (m, 4 H), 8.48 (t, 1 H, J = 2.5 Hz), 9.0 (d, 1 H, J = 2.5 Hz), 9.2 (d, 1 H, J = 2.5 Hz). Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.99; H, 5.79; N, 6.02.

Methyl 5-(2-Methylphenyl)nicotinate (7d). From methyl 5-bromonicotinate (4) and (2-methylphenyl)boronic acid (**11d**),[22] method A gave 0.27 g (12%) and method B gave 1.84 g (81%) of an oil which crystallized on standing: mp 76.5–77.5 °C (hexane); TLC R_f 0.3 (25% EtOAc/hexane); IR (CCl_4) 3000, 2950, 2900, 1730, 1580, 1540, 1430, 1400, 1300, 1280, 1220, 1200, 1160, 1020, 980, 950, 900, 880, 810, 700 cm^{-1}; ^1H NMR (CCl_4) δ 2.3 (s, 3 H), 3.9 (s, 3 H), 7.25, 7.5, (2s, 4 H), 8.3 (d, 1 H, J = 2.5 Hz), 8.7 (d, 1 H, J = 2.5 Hz), 9.2 (d, 1 H, J = 2.5 Hz). Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.72; H, 5.92; N, 6.13.

Methyl 5-(2-Nitrophenyl)nicotinate (7e). From methyl 5-bromonicotinate (4) and (2-nitrophenyl)boronic acid (**11e**),[21] method A gave 0.15 g (6%) and method B gave 1.6 g (61%) of a slightly yellow solid: mp 125–126 °C (Et_2O/CH_2Cl_2); TLC R_f 0.45 (5% EtOAc/CH_2Cl_2); IR ($CHCl_3$), 3050, 1730, 1580, 1540, 1440, 1350, 1310, 1290, 1260, 1230, 1220, 1160, 1110, 960, 910, 840, 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.0 (s, 3 H), 7.2–8.2 (m, 4 H), 8.2 (t, 1 H, J = 2 Hz), 8.8 (d, 1 H, J = 2 Hz), 9.4 (d, 1 H, J = 2 Hz). Anal. Calcd for $C_{13}H_{10}N_2O_4$: C, 60.47; H, 3.90; H, 10.85. Found: C, 60.18; H, 3.72; N, 10.72.

Methyl 5-(2-Methoxyphenyl)nicotinate (7f). From methyl 5-bromonicotinate (4) and (2-methoxyphenyl)boronic acid (**11f**),[22] method B gave 1.7 g (80%) of a white crystalline solid: mp 105–106 °C (Et_2O/hexane); TLC R_f 0.3 (25% EtOAc/hexane); IR ($CHCl_3$) 2980, 2850, 1735, 1590, 1580, 1500, 1460, 1440, 1310, 1280, 1260, 1220, 1180, 1160, 1120, 1060, 1040, 1020, 960, 900, 850, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.85 (s, 3 H), 4.05 (s, 3 H), 7.3–7.6 (m, 4 H), 8.5 (t, 1 H, J = 2.5 Hz), 9.0 (d, 1 H, J = 2.5 Hz), 9.2 (d, 1 H, J = 2.5 Hz). Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 68.86; H, 5.29; N, 5.71.

Methyl 5-(2-Furyl)nicotinate (7h). From methyl 5-bromonicotinate (4) and 2-furanboronic acid (**11h**),[22] method B gave 1.75 g (86%) of white needles: mp 70–71 °C (Et_2O/hexane); TLC R_f 0.40 (25% EtOAc/hexane); IR (CCl_4) 3000, 2950, 1735, 1590, 1500, 1440, 1420, 1300, 1260, 1210, 1150, 1110, 1020, 910, 760, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.0 (s, 3 H), 6.55 (dd, 1 H, J = 2.4 Hz), 6.85 (d, 1 H, J = 4 Hz), 7.6 (d, 1 H, J = 2 Hz), 8.6 (t, 1 H, J = 2 Hz), 9.1 (d, 2 H, J = 2 Hz). Anal. Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 64.60; H, 4.32; N, 6.78.

Methyl 5-(3-Furyl)nicotinate (7i). From methyl 5-bromonicotinate 4 and 3-furanboronic acid (**11i**),[22] method B gave 1.70 g (83%) of white crystals: mp 70–71 °C (Et_2O/hexane); TLC R_f 0.24 (40% EtOAc/hexane); IR ($CHCl_3$) 3050, 1730, 1580, 1560, 1500, 1450, 1440, 1420, 1350, 1320, 1310, 1260, 1205, 1160, 1155, 1105, 1060, 1010, 980, 940, 910, 860, 825, 780, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.0 (s, 3 H), 6.8 (m, 1 H), 7.6 (t, 1 H, J = 2 Hz), 7.95 (m, 1 H), 8.2 (t, 1 H, J = 2 Hz), 9.0 (d, 1 H, J = 2 Hz), 9.2 (d, 1 H, J = 2 Hz). Anal. Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 64.80; H, 4.47; N, 6.76.

General Procedure for the Preparation of the Arylboronic Acids (11). To a rapidly stirred solution of 46 mL (200 mmol) of triisopropylborate (98%) in 2.0 mL of dry THF cooled to −70 °C under a nitrogen atmosphere was added a solution of the arylmagnesium bromide or aryllithium reagent (100 mL, 1–3 M in Et_2O or THF) dropwise over 30 min. The solution was allowed to warm to room temperature and stir 10 min and then partitioned between 250 mL of Et_2O and 250 mL of 10% aqueous HCl. The ethereal extract was washed with water (100 mL) and dried ($MgSO_4$). Removal of solvents under reduced pressure followed by purification by recrystallization from Et_2O/hexane afforded the pure arylboronic acid.

(3-Methylphenyl)boronic Acid (11c). From 100 mmol of (3-methylphenyl)magnesium bromide in Et_2O (concentration determined by titration with standardized *sec*-butyl alcohol in xylene using 1,10-phenanthroline as indicator) and 200 mmol of commercial triisopropylborate (98%), using the general procedure described above, there was obtained 13 g (95%) of (3-methylphenyl)boronic acid: mp 157–158 °C (H_2O).[21]

(2-Methoxyphenyl)boronic Acid (11f). From 100 mmol of (2-methoxyphenyl)magnesium bromide in Et_2O (concentration determined by titration with standardized *sec*-butyl alcohol in xylene using 1,10-phenanthroline as indicator) and 200 mmol of commercial triisopropylborate (98%), using the general procedure described above, there was obtained 12 g (79%) of (2-methoxyphenyl)boronic acid: mp 105–106 °C (H_2O).[22a] This particular boronic acid was kept stored at −10 °C since it slowly decomposed into (2-hydroxyphenyl)boronic acid at room temperature.[22b]

2-Furanboronic Acid (11h). From 100 mmol of 2-furyllithium in 150 mL of hexane/THF, prepared with the procedure described by Arco, Trammel, and White,[33] and 200 mmol of commercial triisopropylborate (98%), using the general procedure described above, there was obtained 10 g (90%) of 2-furanboronic acid: mp 112 °C dec (H_2O); TLC R_f 0.4 (5% EtOAc/CH_2Cl_2).

3-Furanboronic Acid (11i). From 100 mmol of 3-furyllithium[34] in Et_2O (concentrated determined by titration with standardized *sec*-butyl alcohol in xylene using 1,10-phenanthroline as indicator) and 200 mmol of commercial triisopropylborate (98%), using the general procedure described above, there was obtained 9.2 g (82%) of 3-furanboronic acid: mp 127–128 °C (H_2O).[24]

Methyl 5-Bromo-6-chloronicotinate (13). To a stirred suspension of 13.9 g (100 mmol) of 6-hydroxynicotinic acid (Aldrich, 95%) in 25 mL of glacial AcOH was added 7.6 mL (150 mmol) of bromine. The mixture was warmed to 50 °C for 12 h and then concentrated to dryness under reduced pressure. To the crude residue was added 25 mL of $POCl_3$ and 42 g (200 mmol) of PCl_5. The mixture was heated to reflux for 12 h, and then the excess $POCl_3$ was distilled off under reduced pressure (bath temperature kept below 50 °C). The crude brown residue was dissolved in 125 mL of CH_2Cl_2 and 50 mL of MeOH and warmed to reflux for 2 h. The solvents were distilled off under reduced pressure, and the residue was partitioned between ether (200 mL) and saturated aqueous $NaHCO_3$ (75 mL), then dried ($MgSO_4$), and concentrated to dryness under reduced pressure. Purification by flash chromatography[36] on silica gel using 15% EtOAc/hexane gave 20.6 g (82%) of white crystalline solid: mp 77 °C (EtOH); IR and ^1H NMR identical with those reported by Setliff and Reeves for methyl 5-bromo-6-chloronicotinate prepared in a different manner.

Methyl 5-Bromo-6-methoxynicotinate (14). To a stirred solution of 22 mmol of NaOMe from 0.5 g of Na metal in 50 mL of MeOH was added 5 g (20 mmol) of methyl 5-bromo-6-chloronicotinate (13) in 5 mL of MeOH. The initially exothermic reaction was allowed to stir for 30 min and then neutralized with glacial AcOH (1 mL). After concentration under reduced pressure, the residue was partitioned between CH_2Cl_2 (50 mL) and saturated aqueous $NaHCO_3$ (10 mL). The organic extracts was dried ($MgSO_4$) and then concentrated to dryness under reduced pressure. Recrystallization from Et_2O/hexane gave 4.8 g (96%) of white crystalline solid: mp 104–106 °C (Et_2O/hexane); IR (CCl_4) 2960, 1735 (C=O), 1600, 1490, 1445, 1420, 1390, 1315, 1300, 1285, 1270, 1245, 1235, 1225, 1125, 1065, 1020, 980, 940 cm^{-1}; ^1H NMR (CCl_4) δ 3.9 (s, 3 H), 4.0 (s, 3 H), 8.4 (d, 1 H, J = 3 Hz), 8.7 (d, 1 H, J = 3 Hz). Anal. Calcd for $C_8H_8BrNO_3$: C, 39.05; H, 3.28; N, 5.69. Found: C, 39.08; H, 3.24; N, 5.60.

Methyl 5-Bromo-6-(phenylthio)nicotinate (15). A mixture of 1.6 g (6.3 mmol) of the 5-bromo-6-chloronicotinate (13), 0.68 mL of thiophenol, and 1 mL of Et_3N in 20 mL of CH_2Cl_2 was warmed to reflux under a nitrogen atmosphere for 30 min. The resulting mixture was diluted with 50 mL of Et_2O, washed with 5 mL of 10% NaOH and 10 mL of water, and then dried ($MgSO_4$). Removal of solvents under reduced pressure gave 1.8 g (88%) of crystalline product: mp 117–118 °C (Et_2O/hexane); IR ($CHCl_3$)

3070, 3020, 2960, 1730, 1585, 1485, 1450, 1425, 1360, 1300, 1285, 1220, 1100, 1125, 1040, 1030, 1005, 975, 930, 860 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.9 (s, 3 H), 7.5 (m, 5 H), 8.3 (d, 1 H, J = 3 Hz), 8.8 (d, 1 H, J = 3 Hz). Anal. Calcd for $C_{13}H_{10}BrNO_2S$: C, 48.16; H, 3.11; N, 4.32. Found: C, 48.20; H, 3.07; N, 4.23.

4-Bromo-3-cyano-4,6-dimethyl-2(1*H*)-pyridone (17). To a stirred suspension of 50 g (0.3 mol) of 4,6-dimethyl-3-cyano-2-(1*H*)-pyridone (**16**)[26] in 250 mL of glacial AcOH was added dropwise with stirring 25 mL of bromine. The resulting clear solution was allowed to stir for 30 min and then concentrated to dryness under reduced pressure. After recrystallization from aqueous ethanol there was obtained 70 g (95%) of colorless needles: mp 260 °C (EtOH/H_2O);[37] IR (Nujol) 3350, 2250, 1660, 1600, 1530, 1420, 1390, 1320, 1220, 1160, 1050, 1040, 1020, 950, 770 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.4 (s, 3 H), 2.5 (s, 3 H); HMRS calcd for $C_8H_7BrN_2O$ m/e 225.9742, found m/e 227.9730 ± 0.022.

5-Bromo-2-chloro-3-cyano-4,6-dimethylpyridine (18). A stirred solution of 14 g (62 mmol) of pyridone **17**, 13 g (62 mmol) of PCl_5, and 10 mL of $POCl_3$ was heated under reflux for 8 h. The $POCl_3$ was distilled off under reduced pressure and the residue partitioned between CH_2Cl_2 (100 mL) and 5% aqueous NaOH (100 mL). The organic extracts were dried ($MgSO_4$) and then concentrated to dryness under reduced pressure. Purification by recrystallization from Et_2O gave 13 g (86%) of slightly yellow crystals: mp 105–106 °C (Et_2O); IR ($CHCl_3$) 3000, 2250, 1560, 1520, 1420, 1400, 1350, 1270, 1205, 1150, 1000, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.65 (s, 3 H), 2.7 (s, 3 H). Anal. Calcd for $C_8H_6ClBrN_2$: C, 39.14; H, 2.46; N, 11.41. Found: C, 39.12; H, 2.44; N, 11.28.

5-Bromo-3-cyano-4,6-dimethylpyridine (19). A mixture of 14 g (56 mmol) of 5-bromo-2-chloro-3-cyano-4,6-dimethylpyridine, 56 mL of 47% aqueous HI, and 8 g (258 mmol) of red phosphorus was heated to 140 °C for 4 h. After being cooled to 25 °C, the mixture was cautiously poured into 500 mL of saturated aqueous $NaHCO_3$ containing 10 g of Na_2SO_3. The precipitate was collected by vacuum filtration and dissolved in Et_2O (200 mL). The solution was filtered to remove any excess red phosphorus, then dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash chromatography[36] using 10% EtOAc/hexane gave 7.4g (62%) of solid: mp 87.5–88 °C (Et_2O/hexane); IR ($CHCl_3$) 3000, 2225, 1575, 1455, 1425, 1380, 1360, 1240, 1000, 930 cm^{-1}; ^1H NMR (CCl_4) δ 2.6 (s, 3 H), 2.7 (s, 3 H), 8.6 (s, 1 H). Anal. Calcd for $C_8H_7N_2Br$: C, 45.52; H, 3.34; N, 13.27. Found: C, 45.57; H, 3.28; N, 13.25.

Methyl 5-Bromo-4,6-dimethylnicotinate (21). A mixture of 4 g (19 mmol) of nitrile **19**, was heated to reflux in 50 mL of 20% aqueous KOH for 3 days. After being cooled to 25 °C, the mixture was neutralized with concentrated HCl and the solvents were removed under reduced pressure. The remaining solid was extracted with ten 100-mL portions of hot acetone, and the combined extracts were concentrated under reduce pressure to give the acid **19** as an off-white solid (4.5 g): IR (Nujol) 3600–3200, 2800–2350, 1720, 1640, 1290, 1250, 1230, 920, 880, 760 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.7 (s, 6 H), 4.4 (br s, 1 H), 8.85 (s, 1 H); HMRS calcd for $C_8H_8BrNO_2$ (M^+ – 18) m/e 210.9633, found m/e 210.9622 ± 0.021. The crude 5-bromo-4,6-dimethylnicotinic acid (**20**) was dissolved in 10 mL of $SOCl_2$ and warmed to reflux for 4 h under a $CaCl_2$ drying tube. The excess $SOCl_2$ was distilled off under reduced pressure, 30 mL of MeOH was added, and the solution was warmed to reflux for 12 h, and then concentrated to dryness under reduced pressure. The residue was partitioned between 100 mL of CH_2Cl_2 and 25 mL of saturated aqueous $NaHCO_3$, and the combined organic extracts were concentrated under reduced pressure. The product was homogeneous by TLC and crystallized on standing (4 g, 87%): mp 49–50 °C (Et_2O/hexane); TLC R_f 0.28 (15% EtOAc/hexane); IR (CCl_4) 2950, 1720, 1560, 1445, 1420, 1360, 1280, 1240, 1210, 1080, 990, 920 cm^{-1}; ^1H NMR (CCl_4) δ 2.7 (s, 6 H), 3.9 (s, 3 H), 8.7 (s, 1 H). Anal. Calcd for $C_9H_{10}BrNO_2$: C, 44.28; H, 4.13; N, 5.74. Found: C, 44.35; H, 4.04; N, 5.72.

Methyl 5-Phenyl-6-methoxynicotinate (22a). From 10 mmol of methyl 5-bromo-6-methoxynicotinate (**14**) and 15 mmol of phenylboronic acid, method B gave 2.1 g (86%) of white crystals: mp 76–77 °C (Et_2O/petroleum ether, 20–40); TLC R_f 0.30 (10% EtOAc/hexane); IR (CCl_4) 3100, 3060, 3020, 3000, 2960, 2900, 2860, 1730, 1610, 1570, 1500, 1480, 1460, 1450, 1440, 1400, 1370, 1300, 1280, 1270, 1220, 1200, 1180, 1140, 1050, 1020, 975, 940, 915, 880, 850, 730, 700 cm^{-1}; ^1H NMR (CCl_4) δ 3.85 (s, 3 H), 4.0 (s, 3 H), 7.1–7.6 (m, 5 H), 8.2 (d, 1 H, J = 3 Hz), 8.75 (d, 1 H, J = 3 Hz). Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.03; H, 5.47; N, 5.67.

Methyl 5-(2-Furyl)-6-methoxynicotinate 22b. From 10 mmol of methyl 5-bromo-6-methoxynicotinate (**14**) and 15 mmol of 2-furanboronic acid (**11h**), method B gave 1.7 g (73%) of white crystalline solid: mp 78–79 °C (Et_2O/hexane); TLC R_f 0.4 (15% EtOAc/hexane); IR (CCl_4) 2980, 2940, 2900, 2860, 2830, 1730, 1610, 1575, 1500, 1475, 1460, 1435, 1420, 1390, 1370, 1300, 1275, 1240, 1225, 1210, 1190, 1160, 1120, 1050, 1015, 930, 885, 800, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.0 (s, 3 H), 4.2 (s, 3 H), 6.5 (dd, 1 H, J = 2, 3 Hz), 7.0 (d, 1 H, J = 3 Hz), 7.5 (d, 1 H, J = 2.5 Hz), 8.6 (d, 1 H, J = 2.5 Hz), 8.7 (d, 1 H, J = 2.5 Hz). Anal. Calcd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.64; H, 4.59; N, 5.88.

Methyl 5-(2-Methoxyphenyl)-6-methoxynicotinate (22c). From 10 mmol of methyl 5-bromo-6-methoxynicotinate (**14**) and 15 mmol of 2-methoxyphenylboronic acid (**11f**), method B gave 1.64 g (60%) of a thick oil: IR (CCl_4) 3000, 2960, 2900, 2840, 1730, 1600, 1590, 1580, 1500, 1480, 1460, 1440, 1400, 1305, 1285, 1270, 1265, 1240, 1210, 1200, 1185, 1165, 1125, 1060, 1040, 1020, 970, 940, 885, 870, 850, 840, 730 cm^{-1}; ^1H NMR (CCl_4) δ 3.70 (s, 3 H), 3.85 (s, 3 H), 3.95 (s, 3 H), 6.7–7.3 (m, 4 H), 8.0 (d, 1 H, J = 2.5 Hz), 8.7 (d, 1 H, J = 2.5 Hz). Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.12. Found: C, 65.57; H, 5.33; N, 5.17.

Methyl 5-Phenyl-6-(phenylthio)nicotinate (23). From 10 mmol of methyl 5-bromo-6-(phenylthio)nicotinate and 15 mmol of phenylboronic acid, method B gave 0.834 g (26%) of white crystalline solid: mp 123–124 °C (Et_2O); TLC R_f 0.22 (15% EtOAc/hexane); IR (CCl_4) 3070, 3060, 2960, 2890, 1730, 1575, 1480, 1440, 1425, 1410, 1405, 1360, 1290, 1280, 1250, 1230, 1210, 1120, 1050, 1025, 1000, 980, 940, 865 cm^{-1}; ^1H NMR (CCl_4) δ 3.85 (s, 3 H), 7.4 (m, 10 H), 8.0 (d, 1 H, J = 2 Hz), 8.75 (d, 1 H, J = 2 Hz). Anal. Calcd for $C_{19}H_{15}NO_2S$: C, 71.01; H, 4.70; N, 4.36. Found: C, 71.08; H, 4.77; N, 4.40.

Methyl 4,6-Dimethyl-5-phenylnicotinate (24). From 10 mmol of methyl 5-bromo-4,6-dimethylnicotinate (**21**) and 15 mmol of phenylboronic acid, method B gave 2.1 g (87%) of a thick, colorless oil: TLC R_f 0.40 (30% EtOAc/hexane); IR ($CHCl_3$) 3010, 2950, 1725, 1580, 1435, 1305, 1260, 1200, 1085, 1010, 990, 935, 910, 720, 700 cm^{-1}; ^1H NMR (CCl_4) δ 2.25 (s, 6 H), 3.9 (s, 3 H), 7.0–7.6 (m, 5 H), 8.85 (s, 1 H). Anal. Calcd for $C_{15}H_{15}NO_2$: C 74.67; H, 6.26; N, 5.80. Found: C, 74.59; H, 6.19; N, 5.81.

Methyl 5-(3-Aminophenyl)nicotinate (3). A solution of 5 g (20 mmol) of methyl 5-(3-nitrophenyl)nicotinate in 50 mL of MeOH and 50 mL of MeOAc was shaken with 0.5 g of 5% palladium on carbon under 50 psi of hydrogen for 8 h. The solution was filtered then concentrated under reduced pressure. Purification by evaporative distillation at 150 °C (0.05 mm) gave 4.47 g (96%) of a thick colorless oil which crystallized on standing: mp 93–94.5 °C (Et_2O/hexane); IR ($CHCl_3$) 3500, 3420, 3000, 1730, 1620, 1590, 1500, 1460, 1440, 1400, 1330, 1310, 1270, 1210, 1160, 1110, 1050, 1020, 980, 900, 860, 820, 690, 650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.9 (br s, 2 H), 6.7–7.5 (m, 4 H), 8.55 (t, 1 H, J = 2 Hz), 9.0 (d, 1 H, J = 2 Hz), 9.2 (d, 1 H, J = 2 Hz). Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.14; H, 5.36; N, 12.22.

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93350-07-3; $Pd(PPh_3)_4$, 14221-01-3; $Pd(OAc)_2$, 3375-31-3; NaOMe, 124-41-4; (2-methoxyphenyl)magnesium bromide, 16750-63-3; thiophenol, 108-98-5; phenylboronic acid, 98-80-6; 6-hydroxynicotinic acid, 5006-66-6; methyl nicotinate, 93-60-7; 3,3′-dinitrobiphenyl, 958-96-3; nicotinic acid, 59-67-6; tri-*o*-tolylphosphine, 6163-58-2; toluene, 108-88-3; triisopropylborate, 5419-55-6; (3-methylphenyl)magnesium bromide, 28987-79-3; 2-furyllithium, 2786-02-9; 3-furyllithium, 53101-93-2.

A High-Yield Modification of the Pschorr Phenanthrene Synthesis

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A relationship between substituents on the aryl ring undergoing homolytic aromatic substitution and the yield of Pschorr reaction product has been demonstrated. The new variation in which a (phenylsulfonyl)oxy group is present on the acceptor ring has been used to synthesize several highly oxygenated 9-phenanthrenecarboxylic acids in significantly improved yields.

Since the initial report[1] of the use of an arenediazonium salt to effect intramolecular coupling and yield 9-phenanthrenecarboxylic acid, the Pschorr reaction has been very widely used and reviewed.[2] Stimulation for these studies has been, in part, provided by the fact that many naturally occurring compounds of biological and therapeutic interest contain a phenanthrene or reduced phenanthrene ring system.[2,3] A number of alternative methods have been developed to synthesize the phenanthrene ring system, but the Pschorr reaction remains the primary method.

A survey of the literature on the Pschorr reaction revealed the following salient points: (1) the reactive intermediate was an aryl radical resulting from the corresponding arenediazonium salt; (2) methodology has been reported for the preparation, handling, and decomposition of the arenediazonium salts to afford the intermediate aryl radical; (3) substituents on the aromatic ring being attacked always resulted in lower coupled yields than in the unsubstituted case. No clear relationship between the inductive effect, number, or position of substituents and the yields of coupled products has been demonstrated with the classical methods used for the decomposition of arenediazonium salts (copper, copper salts, thermolysis, zinc, and sodium hypophosphite).

Finally, the report[4] that iodide ion cleanly effected Pschorr coupling of the corresponding diazonium salts of (*E*)-2-amino-α-phenylcinnamic acid, and especially several of its derivatives, represents a synthetically useful, homogeneous, and convenient alternative to the previously reported methods for ring closure via arenediazonium salts. Of particular interest is the fact that consistently higher yields of substituted phenanthrenes were reported than by previous authors who decomposed the same diazonium salts with Gatterman copper according to the original procedure.[1]

The intermediacy of aryl radicals in the Pschorr reaction has been well documented.[2,5] Recent reports of newer methods[5d,e,6] of reacting arenediazonium salts in the Pschorr reaction merely represent new techniques for producing aryl radicals. Since it would be the same radical being formed, these changes in the immediate environment of the aryl radical have not resulted in any significant improvement of coupling yields as compared to the oxidation of iodide ion by arenediazonium salts. The mechanism of the oxidation of iodide ion and reduction of arenediazonium salts, which ultimately yields molecular nitrogen and the corresponding aryl radical, was understood[5a,d–f] long before the first applications to the intramolecular Pschorr synthesis of phenanthridones[7] and phenanthrenes.[4]

With the reported sodium iodide mediated Pschorr phenanthrene synthesis, consistent data became available demonstrating a relationship between the inductive effect of substituents on the aryl ring undergoing homolytic aromatic substitution and the yield of intramolecularly coupled product. However, the isolated yields of phenanthrenes were reported to drop by about 10% for every methyl or methoxy substituent. Since most natural products, and their derivatives and degradation products, which are of interest are highly methoxy substituted, this application of the Pschorr reaction to the synthesis of such phenanthrenes has resulted in comparatively low yields.

We now demonstrate improved coupling yields in the Pschorr phenanthrene synthesis by substituting the electron-withdrawing (phenylsulfonyl)oxy group for electron-donating alkoxy groups in two systems, a dioxygenated and a trioxygenated α-phenyl group of the corresponding di-

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