Synthesis of Regioisomeric 6,9-(chlorofluoro)-Substituted Benzo[*g*]quinoline-5,10-diones, Benzo[*g*]isoquinoline-5,10-diones and 6-Chloro-9-fluorobenzo[*g*]quinoxaline-5,10-dione

A. Paul Krapcho*, Cynthia E. Gallagher, Abdelhakim Hammach and Michael Ellis

Department of Chemistry, University of Vermont, Burlington VT 05405

Ernesto Menta and Ambrogio Oliva

Boehringer Mannheim Italia, Research Center, 20052, Monza, Italy

Received June 14, 1996

Treatment of difluoro or chloro fluoro-substituted benzyl bromides **5a-c** with zinc dust in tetrahydrofuran leads to the corresponding benzylic zinc bromides **6a-c**. These organometallics on treatment with chlorosubstituted heterocyclic esters **4A** and **4B** mediated by nickel catalysis undergo couplings to yield dihalobenzyl substituted heterocyclic esters **7Aa-c** and **7Ba-c**. Treatment of **4c** with **6c** under Pd catalysis leads to **7Cc**. The acids **8**, prepared by hydrolysis of these esters, with treatment of fuming sulfuric acid undergo cyclizations and oxidations to yield the desired regioisomeric dihalo-substituted heterocyclic quinones **2**.

J. Heterocyclic Chem., **34**, 27 (1997).

Recently we have reported the synthesis of 6,9-bis-[(aminoalkyl)amino]-substituted benzo[*g*]quinolines **1A** [1,2], benzo[*g*]isoquinolines **1B** [3] and benzo[*g*]quinoxalines **1C** [4] in which both distal side arms were identical (R = R_1). These analogues were prepared by sequential ipso displacements (S_NAr) of the nucleofugal fluorides from the 6,9-difluoro-substituted benzo[*g*]quinoline **2Aa**, benzo[*g*]isoquinoline **2Ba** and benzo[*g*]quinoxaline **2Ca**, respectively. Analogue **1B** (R = R_1 = $(CH_2)_2NH_2$) exhibits outstanding antitumor activity against a number of cell lines [3] (Figure 1).

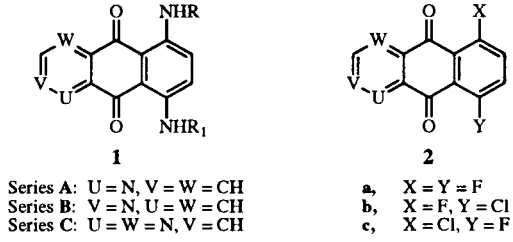


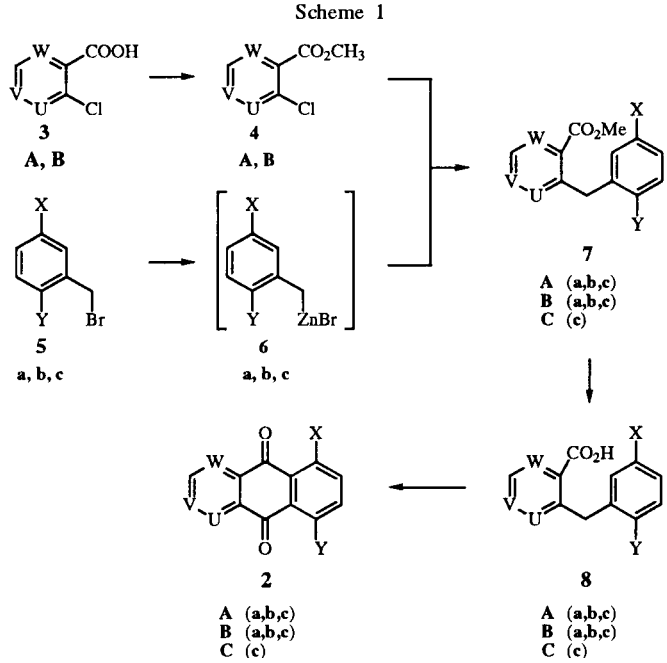
Figure 1

In a continuation of our efforts to develop new antitumor agents and to probe more deeply into the cell killing mechanisms of the aza bioisosteres **1A**, **1B** and **1C**, we wished to prepare analogues related to these chemotypes but holding different side arms at the 6 and 9 positions (R different from R_1). These molecules were desired for a study of the interactions with DNA for comparisons with chemotypes with identical distal side arms.

Although mono substitution of fluoride from 6,9-difluorobenzo[*g*]isoquinoline (**1Ba**) with several amino nucleophiles was regioselective, difficulties were encountered in the separation of the regioisomers. For example, a 2:1 ratio of mono substitution products was obtained on treatment of **1Ba** with *N,N*-dimethylethylenediamine, presumably the major regioisomer resulting from displacement of the C-6 fluoride.

We now wish to report the synthesis of regioisomeric chlorofluorobenzo[*g*]quinolines **2Ab** and **2Ac**, benzo[*g*]-isoquinolines **2Bb** and **2Bc** and 6-chloro-9-fluorobenzo-[*g*]quinoxaline **2Cc**. In these molecules, the fluoride would readily undergo an S_NAr displacement at room temperature at a rate considerably more rapid than the chloride on being treated with amine nucleophiles. The mono-substituted chloro compound being treated at a higher temperature with a different amine (or any other nucleophilic species) would lead to the desired derivatives.

Scheme 1



The synthesis share a common pathway which is outlined in Scheme 1.

The 3-chloroisonicotinic acid (**3B**) was obtained by treatment of 3-chloropyridine with lithium diisopropylamide in THF at -78° followed by bubbling carbon dioxide gas into the 4-lithio-3-chloropyridine [5]. Treatment of acids **3A** and **3B** with ethereal diazomethane led to the esters **4A** (84%) and **4B** (70%), respectively.

The α-bromo-2-chloro-5-fluorotoluene (**5b**) and α-bromo-2-fluoro-5-chlorotoluene (**5c**) were prepared by treatment of 2-chloro-5-fluorotoluene or 2-fluoro-5-chlorotoluene with *N*-bromosuccinimide in refluxing carbon tetrachloride in the presence of a trace of dibenzoyl peroxide.

Since benzylic zinc bromides are easily prepared [6-8], treatment of benzylic bromides **5a-c** in tetrahydrofuran with activated zinc led to the corresponding benzylic zinc bromides **6a-c**.

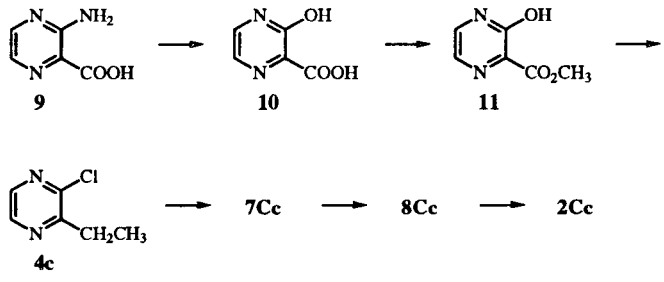
The crucial step involved the coupling of organo zinc bromides **6** with the nicotinate esters **4A** and isonicotinate esters **4B** mediated by nickel or palladium catalysis [9-15]. Addition of benzylic zinc bromides **6a, 6b** or **6c** to **4A** in the presence of dichlorobis[triphenylphosphine]nickel (or [1,2-bis(diphenylphosphino]ethane]dichloronickel(II) in the case of **7Ac**) in tetrahydrofuran as the solvent led to the methyl-2-benzylic substituted nicotinates **7Aa** (86%), **7Ab** (65%) and **7Ac** (63%), respectively. Similarly the organo zinc reagents **6a, 6b** and **6c** coupled with isonicotinate ester **4B** to afford methyl-3-benzylic isonicotinate **7Ba** (52%), **7Bb** (65%) and **7Bc** (65%), respectively.

The nicotinate esters **7Aa-c** and isonicotinate esters **7Ba-c** were hydrolyzed to the corresponding nicotinic acids **8Aa-c** (79-96%) and isonicotinic acids **8Ba-c** (70-95%). The cyclization of these acids and oxidation of the expected azaanthrone (or azaanthranol) intermediates to the desired aza diones **2** was accomplished in one operational step by heating the acids in fuming sulfuric acid. Thus, on heating the 2-benzyl substituted nicotinate acids **8Aa-c** in fuming sulfuric acid (27-33% free sulfur trioxide), the benzo[*g*]quinoline diones **2Aa-c** were obtained in reasonable yields (41-54%). On heating the 3-benzyl substituted isonicotinic acids **8Ba-c** In fuming sulfuric acid (18-24% sulfur trioxide), the benzo[*g*]isoquinoline diones **2Ba-c** (31-55%) were obtained.

The preparation of the pyrazine ester **4C** is illustrated in Scheme 2.

The 3-aminopyrazine-2-carboxylic acid **9** was converted into 3-hydroxypyrazine-2-carboxylic acid (**10**) by diazotization and heating the resultant diazonium salt in water [16]. Acid **10** was converted into the pyrazine ester **11** using dry hydrogen chloride in methanol [17]. The chloro ester **4c** was obtained by treatment of **11** with phosphorus oxychloride [17]. Treatment of the organo zinc reagent derived from **5c** with pyrazine ester **4c** in the presence of dichlorobis[triphenylphosphine)palladium afforded **7Cc**. Hydrolysis of this ester led to the acid **8Cc** which on heating in fuming-sulfuric acid led to the desired 6-chloro-9-fluorobenzo[*g*]quinoxaline **2Cc** (35%).

Scheme 2



Conclusions.

The synthetic pathway which is described should prove useful for the regioselective synthesis of other substituted analogues related to the heterocycles described here. This procedure avoids the problem of Hayashi type rearrangements [18] found during the cyclizations of keto acids. The displacement studies of the chloro fluoro substituted analogues **2** with a variety of nucleophiles will be reported in the near future.

EXPERIMENTAL

Melting points were determined on a Thomas Hoover or a Fisher-Johns apparatus and are uncorrected. The nmr spectra were recorded on a Brucker WP-270SY, WM-250 pulsed FT spectrometer. Elemental analysis were performed by Robertson Microlit laboratories, Inc. in Madison, NJ. The tetrahydrofuran and diisopropylamine were freshly distilled from potassium metal and calcium hydride, respectively. The α-bromo-2,5-difluorotoluene (**5a**), 2-chloronicotinic acid (**3A**), 3-aminopyrazine-2-carboxylic acid (**9**), [1,2-bis(diphenylphosphino)ethane]nickel(II) chloride were purchased from Aldrich. The 2-fluoro-5-chlorotoluene, 2-chloro-5-fluorotoluene, dichlorobis[triphenylphosphine]nickel and tetrakis[triphenylphosphine]palladium were obtained from Lancaster.

The activated zinc was prepared according to a literature procedure [19]. The preparations of the organo zinc reagents and the coupling procedures were performed under nitrogen atmospheres.

Dihalobenzo[*g*]quinoline-5,10-diones **2Aa-c**, Dihalobenzo[*g*]-isoquinoline5,10-diones **2Ba-c** and 6-Chloro-9-fluorobenzo[*g*]-quinoxaline-5,10-dione **2Cc**. Procedure.

A mixture of the appropriate acid **8** (0.20 mmole) in fuming sulfuric acid (0.4 ml, 27-33% free sulfur trioxide) was heated for 3 hours at 130-135° in an oil bath. The dark reddish-brown solution was quenched over ice (10 g) and the mixture extracted with dichloromethane (20 ml). The aqueous layer was cautiously neutralized by the addition of solid sodium bicarbonate and extracted with dichloromethane (3 x 15 ml). The combined extracts were dried over magnesium sulfate and the solvent removed by rotary evaporation to yield the products as tan or

yellow solids. Chromatography over silica gel using ethyl acetate as eluant led to yellow solids.

6,9-Difluorobenzo[*g*]quinoline-5,10-dione (**2Aa**).

This compound was obtained as a pale yellow solid (53%), mp 250-251° dec, lit [2] mp 251-252°; ^{1}H nmr (deuteriochloroform): δ 9.12 (dd, J = 4.5 Hz, J = 1.6 Hz, 1H), 8.60 (dd, J = 7.9 Hz, J = 1.6 Hz, 1H), 7.75 (dd, J = 7.9 Hz, J = 4.5 Hz, 1H), 7.54 (m, 2H); ^{13}C nmr (deuteriochloroform): δ 179.9 (s), 178.5 (s), 157.8 (d, J_{CF} = 270 Hz), 157.5 (d, J_{CF} = 268 Hz), 155.3 (s), 148.1 (s), 135.3 (s), 130.2 (s), 128.0 (s), 125.1 (dd, J_{CCF} = 25 Hz, J_{CCCF} = 9 Hz), 125 (dd, J_{CCF} = 25 Hz, J_{CCCF} = 9 Hz), 121.1 (dd, J_{CCF} = 69 Hz, J_{CCCF} = 5 Hz).

6-Fluoro-9-chlorobenzo[*g*]quinoline-5,10-dione (**2Ab**).

The dione was obtained as a yellow solid (41%), mp 187-188°; ^{1}H nmr (deuteriochloroform): δ 9.11 (dd, J_{HH} = 4.6 Hz, J_{HH} = 1.6 Hz, 1H), 8.58 (dd, J_{HH} = 8.0 Hz, J_{HH} = 1.6 Hz, 1H), 7.81 (dd, J_{HH} = 9.0 Hz, J_{HF} = 4.4 Hz, 1H), 7.74 (dd, J_{HH} = 8.0 Hz, J_{HH} = 4.6 **Hz**, 1H), 7.46 (dd, J_{HF} = 10 Hz, J_{HH} = 9.0 Hz, 1H).

Anal. Calcd. for $C_{13}H_5ClFNO_2$: C, 59.68; H, 1.93; N, 5.35. Found: C, 59.95; H, 2.30; N, 4.97

6-Chloro-9-fluorobenzo[*g*]quinoline-5,10-dione (**2Ac**).

This product was obtained as a pale yellow solid (54%), mp 187-188°; ^{1}H nmr (deuteriochloroform): δ 9.10 (dd, J_{HH} = 4.5 Hz, J_{HH} = 1.5 Hz, 1H), 8.57 (dd, J_{HH} = 8.0 Hz, J_{HH} = 1.5 Hz, 1H), 7.80 (dd, J_{HH} = 8.0 Hz, J_{HH} = 4.5 Hz, 1H), 7.74 (dd, J_{HH} = 9.0 Hz, J_{HF} = 4.5 Hz. 1H), 7.46 (dd, J_{HF} = 10 Hz. J_{HH} = 9.0 Hz, 1H).

Anal. Calcd. for $C_{13}H_5ClFNO_2$: C, 59.68; H, 1.93; N, 5.35. Found: C, 59.90; H, 2.34; N, 5.00.

6,9-Difluorobenzo[*g*]isoquinoline-5,10-dione (**2Ba**).

The acid **8Ba** was heated for 30 minutes at 135° in fuming sulfuric acid (18-24% free sulfur trioxide) and worked up as in the general procedure to yield the product as a pale yellow solid (46%), mp 197-198°, lit [1] 199-200°, identical nmr to that recorded previously.

6-Fluoro-9-chlorobenzo[*g*]isoquinoline-5,10-dione (**2Bb**).

The acid **8Bb** was heated for 0.5 hours at 110-115° in fuming sulfuric acid (18-24% free sulfur trioxide) and worked up as in the general procedure to yield a yellow-brown product (55%), mp 174-175°; ^{1}H nmr (deuteriochloroform): δ 9.54 (s, 1H), 9.10 (d, J_{HH} = 5.0 Hz, 1H), 8.0 (d, J_{HH} = 5.0 Hz, 1H), 7.84 (dd, J_{HH} = 9.0 Hz, J_{HF} = 4.4 Hz, 1H), 7.46 (d, J_{HF} = 9.8 Hz, J_{HH} = 9.0 Hz, 1H).

Anal. Calcd. for $C_{13}H_5ClFNO_2$: C, 59.68; H, 1.93; N, 5.35. Found: 60.00; H, 2.33; N, 4.98.

6-Chloro-9-fluorobenzo[*g*]isoquinoline-5,10-dione (**2Bc**).

The acid **8Bc** in fuming sulfuric acid (18-24% sulfur trioxide) was heated for 40 minutes at 125-130° and worked up as in the general procedure to afford a tan solid (75%). Purification by column chromatography over silica gel using dichloromethane followed by 5:95 to 10:90 to 20:80 mixtures of ethyl acetate:dichloromethane led to the product as a bright yellow solid (55%), mp 226-227°; ^{1}H nmr (deuteriochloroform): δ 9.55 (s, 1H), 9.11 (d, J_{HH} = 5.1 Hz, 1H), 8.10 (d, J_{HH} = 5.1 Hz, 1H), 7.82 (dd, J_{HH} = 9.0 Hz, J_{HF} = 4.4 Hz, 1H), 7.48 (dd, J_{HH} = 9.0 Hz, J_{HF} = 9.2 Hz, 1H)

Anal. Calcd. for $C_{13}H_5ClFNO_2$: C, 59.68; H, 1.93; N, 5.35. Found: C, 59.29; H, 1.93; N, 5.15.

6-Chloro-9-fluorobenzo[*g*]quinoxaline-5,10-dionc (**2Cc**).

Following the procedure described for **2Bc** with heating for 1 hour, this compound was obtained from **8Cc** as a yellow solid (35%), mp 232-234°; ^{1}H nmr (deuteriochloroform): δ 9.1 (s, 2H), 7.88 (dd, J_{HH} = 9 Hz, J_{HF} = 9 Hz, 1H), 7.51 (dd, J_{HH} = 9 Hz, J_{HF} = 4.4 Hz, 1H)

Anal. Calcd. for: $C_{12}H_4ClFN_2 \cdot 0.25\ H_2O$: C, 53.91; H, 1.60; N, 10.48: Found: C, 54.06; H, 1.85; N, 10.14.

3-Chloroisonicotinic Acid (**3B**).

Diisopropylamine (2.7 g, 0.027 mole) and tetrahydrofuran (125 ml) were placed in a 250 ml 3-necked flask and cooled to -78° in a dry ice-acetone bath. A solution of *n*-butyllithium (17.0 ml, 1.6 *M* in hexane) was added *via* syringe over a 10 minute period and the mixture stirred in the bath for 20 minutes. A solution of 3-chloropyridine (3.0 g, 0.027 mole) in tetrahydrofuran (12 ml) was added *via* cannula over a 10 minute period and the resultant yellow solution was stirred for 20 minutes. Carbon dioxide gas, scrubbed by passage through a cold trap at -50°, was bubbled into the mixture at -78° for 1 hour and the mixture was allowed to warm to room temperature. The pale yellow mixture was concentrated to dryness and water (20 ml) was added. The white precipitate which formed on acidification to *p*H 2 with 15% hydrochloric acid was collected by filtration and dried to afford 2.9 g (68%). The crude material was recrystallized from isopropyl alcohol to yield **3B** as feathery white crystals mp 227-228°; lit [20] mp 228-230°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 14.05 (br s, 1H), 8.75 (s, 1H), 8 63 (d, J_{HH} = 5.0 Hz, 1H), 7.70 (d, J_{HH} = 5.0 Hz, 1H).

Methyl-2-Chloronicotinate (**4A**).

An ethereal-ethanol solution of diazomethane was added to a suspension of 2-chloronicotinic acid (**3A**) (1.5 g, 0.095 mole) in methanol (8 ml) until the evolution of nitrogen gas ceased. Removal of the solvents by rotary evaporation led to the crude ester as a pale yellow oil. Distillation under reduced pressure led to **4A** as a colorless liquid, 1.1 g (84%), bp 65-70° at 0.1 mm, which solidified in the freezer, lit [21] mp 23°; ^{1}H nmr (deuteriochloroform): δ 8.52 (dd, J = 4.8 Hz, J = 2.0 Hz, 1H), 8.16 (dd, J = 7.7 Hz, J = 2.0 Hz, 1H), 7.33 (dd, J = 7.7 Hz, J = 4.8 Hz, 1H), 3.96 (s, 3H).

Methyl-3-Chloroisonicotinate (**4B**).

An ethereal solution of diazomethane was added to a suspension of **3B** (200 mg, 1.2 mmoles) in ether (4 ml) until the evolution of nitrogen ceased. The pale yellow solution was decanted from a small amount of insoluble residue and concentrated to yield the ester as a crude yellow oil, 150 mg (70%) which darkened on standing in air; ^{1}H nmr (deuteriochloroform): δ 8.72 (s, 1H), 8.59 (d, J_{HH} = 5.0 Hz, 1H), 7.65 (d, J_{HH} = 5 0 Hz, 1H), 3.98 (s, 3H).

Methyl 3-Chloropyrazine-2-carboxylate (**4c**).

A mixture of **11** (0.60 g, 0.004 moles), phosphorus oxychloride (6.0 g, 0.04 moles) and 1 drop of 10 *N* hydrochloric acid was refluxed for 3 hours. The brown solution was cooled to room temperature and then taken nearly to dryness at 70° in a vacuum. The brown residue was poured onto ice (12 g), the *p*H adjusted to 6 by the addition of concentrated ammonium hydroxide and the residue was extracted with ethyl acetate (4 x 15 ml). The combined extracts were dried over magnesium

sulfate and the solvent was removed by rotary evaporation. The brown residue was distilled (70°, 2 mm Hg) to give the product as a white solid, 0.325 9 (48%), mp 34-35° lit [21] 32°; ^{1}H NMR (deuteriochloroform): δ 8.62 (d, J = 2 Hz, 1H), 8.50 (d, J = 2 Hz, 1H), 4.04 (s, 3H).

α-Bromo-2-chloro-5-fluorotoluene (**5b**).

A suspension of *N*-bromosuccinimide (5.34 g, 30 mmoles), 2-chloro-5-fluorotoluene (4.0 g, 28 mmoles) and dibenzoyl peroxide (100 mg) in carbon tetrachloride (40 ml) was heated at reflux for 3 hours. At the end of this period, the mixture was cooled to room temperature and the succinimide was removed by filtration. The colorless filtrate was concentrated to a pale yellow oil which was distilled under reduced pressure, bp 65-66° (2 mm), to yield a lachrymatory colorless liquid, 5.1 g (82%). Traces of aromatic impurities were detectable in the ^{1}H nmr spectrum; ^{1}H nmr (deuteriochloroform): δ 7.35 (m, 1H), 7.17 (m, 1H), 6.99 (m, 1H), 4.53 (s, 2H).

α-Bromo-2-fluoro-5-chlorotoluene (**5c**).

A mixture of *N*-bromosuccinimide (12.9 g, 73 mmoles), 2-fluoro-5-chlorotoluene (10 g, 69.2 mmoles) and dibenzoyl peroxide (250 mg) in carbon tetrachloride (100 ml) was heated at reflux for 5 hours. The mixture was cooled to room temperature and the succinimide was removed by filtration. The filtrate was washed with cold water (2 x 25 ml) and dried over magnesium sulfate. The solvent was removed under reduced pressure to yield a lachrymatory, clear colorless oil, 13 g (88%) [22]. This crude material was satisfactory for use in the coupling reactions. Distillation of the crude product under reduced pressure, bp 44-45° (0.5 mm), led to material with only trace contamination by the α,α-dibromo analogue; ^{1}H nmr (deuteriochloroform): δ 7.37 (m, 1H), 7.26 (m, 1H), 7.00 (m, 1H), 4.44 (s, 2H).

Methyl 2-(2,5-Dihalobenzyl)nicotinates **7Aa-c**, Methyl 2-(2,5-Dihalobenzyl)isonicotinates **7Ba-c** and Methyl 2-(2-Fluoro-5-chlorobenzyl)pyrazine-3-carboxylate **7Cc**. General Procedure.

A solution of the appropriately substituted benzylic bromide **5** (2.3 mmoles) in tetrahydrofuran (2.5 ml) was added dropwise to activated zinc (2.8 mmoles) in tetrahydrofuran (1.0 ml) at 0° and the mixture was stirred at this temperature for 3 to 4 hours. The zinc reagent was added *via* cannula under a slight nitrogen pressure to either **4A**, **4B** or **4c** (1.6 mmoles) and the catalyst dichlorobis[triphenylphosphine]nickel (0.30 mmole) in tetrahydrofuran (20 ml). The mixture was stirred at room temperature for 3 hours and the resultant brown mixture was quenched with aqueous ammonium chloride (10%, 9 ml) and ethyl acetate (20 ml) was added. The organic layer was washed with brine (2 x 10 ml) and dried over sodium sulfate. The solvents were removed by rotary evaporation to afford a yellow oil which was purified by chromatography over silica gel using hexane:ethyl acetate 4:1 as eluent. The product could be recrystallized from hexane.

Methyl 2-(2,5-Difluorobenzyl)nicotinate (**7Aa**).

This ester was obtained as a white solid (86%), mp 44-45°; ^{1}H nmr (deuteriochloroform): δ 8.68 (dd, J_{HH} = 4.8 Hz, J_{HH} = 1.8 Hz, 1H), 8.22 (dd J_{HH} = 7.8 Hz, J_{HH} = 1.8 Hz, 1H), 7.27 (dd, J_{HH} = 7.8 Hz, J_{HH} = 4.8 Hz, 1H), 6.97 (m, 1H), 6.85 (m, 1H), 6.74 (m, 1H), 4.57 (s, 2H), 3.88 (s, 3H).

Anal. Calcd. for $C_{14}H_{11}F_2NO_2$: C, 63.87; H, 4.21: N, 5.32. Found: C, 63.63; H, 4.19; N, 5.15.

Methyl 2-(2-Chloro-5-fluorobenzyl)nicotinate (**7Ab**).

The reaction mixture was allowed to stir for 48 hours to afford this compound after chromatography as a white solid (65%), mp 44-45°; ^{1}H nmr (deuteriochloroform): δ 8.68 (dd, J_{HH} = 4.8 Hz, J_{HH} = 1.8 Hz, 1H), 8.25 (dd, J_{HH} = 7.9 Hz, J_{HH} = 1.8 Hz, 1H), 7.30 (m, 2H), 6.85 (ddd, J_{HH} = 8.4 Hz, J_{HF} = 8.4 Hz, J_{HH} =3.0 Hz, 1H), 6.63 (dd, J_{HF} = 9.5 Hz, J_{HH} = 3 0 Hz, 1H), 4.65 (s, 2H), 3.84 (s, 3H).

Anal. Calcd. for $C_{14}H_{11}ClFNO_2$: C, 60.12; H, 3.96; N, 5.01. Found: C, 60.22; H, 3.83; N, 4.82.

Methyl 2-(2-Fluoro-5-chlorobenzyl)nicotinate (**7Ac**).

Following the general procedure but with [1,2-bis(diphenylphosphino)ethane]nickel(II)chloride as catalyst and stirring for 24 hours, this compound was obtained as a white solid (63%), mp 48-49°; ^{1}H nmr (deuteriochloroform): δ 8.67 (dd, J_{HH} = 4.8 Hz, J_{HH} = 1.8 Hz, 1H), 8.22 (dd, J_{HH} = 8.0 Hz, J_{HH} = 1.8 Hz, 1H), 7.27 (dd, J_{HH} = 8.0 Hz, J_{HH} = 4.8Hz, 1H), 7.13 (ddd, J_{HH} = 9.0 Hz, J_{HF} = 4.3 Hz, J_{HH} = 2.7 Hz, 1H), 7.03 (dd, J_{HF} = 6.4 Hz, J_{HH} = 2.7 Hz, 1H), 6 96 (dd, J_{HH} = 9.0Hz, J_{HF} = 9.0 Hz, 1H), 4.56 (s, 2H), 3.89 (s, 3H).

Anal. Calcd. for $C_{14}H_{11}ClFNO_2$: C, 60.12; H, 3.96; N, 5.01. Found: C, 59.96; H, 3.86; N, 4.92.

Methyl 3-(2,5-Difluorobenzyl)isonicotinate (**7Ba**).

Following the general procedure, this product was isolated as a white solid (50%), mp 40-42°; ^{1}H nmr (deuteriochloroform): δ 8.67 (br m, 2H), 7.74 (br s, 1H), 7.00 (m, 1H), 6.87 (m, 1H), 6.71 (m, 1H), 4.36 (s, 2H), 3.88 (s, 3H).

Anal. Calcd. for $C_{14}H_{11}F_2NO_2$: C, 63.87; H, 4.21; N, 5.32. Found: C, 63.37; H, 4.30; N, 5.25.

Methyl-3-(2-Chloro-5-fluorobenzyl)isonicotinate (**7Bb**).

Following the general procedure, this product was obtained as a white solid (65%), mp 44-45°; ^{1}H nmr (deuteriochloroform): δ 8.64 (d, J_{HH} = 5.0 Hz, 1H), 8.47 (s, 1H), 7.74 (d, J_{HH} = 5.0 Hz, 1H), 7.34 (dd, J_{HH} = 8.8 Hz, J_{HF} = 5.2 Hz, 1H), 6.88 (ddd, J_{HH} = 8.8 Hz, J_{HF} = 8.3 Hz, J_{HH} = 3.0 Hz, 1H), 6.61 (dd, J_{HF} = 9.3 Hz, J_{HH} = 3.0 Hz, 1H), 4.43 (s, 2H), 3.86 (s, 3H).

Anal. Calcd. for $C_{14}H_{11}ClFNO_2$: C, 60.12; H, 3.96: N, 5.01. Found: C, 59.91; H, 4.01; N, 4.89.

Methyl 3-(2-Fluoro-5-chlorobenzyl)isonicotinate (**7Bc**).

This compound was obtained as a white solid (65%), mp 56-57°; ^{1}H nmr (deuteriochloroform): δ 8.64 (d, J_{HH} = 4.5 Hz, 1H), 8.58 (s, 1H), 7.72 (d, J_{HH} = 4.5 Hz, 1H),7.15 (m, 1H), 7.00 (m, 2H), 4.34 (s, 2H), 3.88 (s, 3H).

Anal. Calcd. for $C_{14}H_{11}ClFNO_2$: C, 60.12; H, 3.96; N, 5.01. Found: C, 60.01; H, 3.85; N, 4.94.

Methyl 2-(2-Fluoro-5-chlorobenzyl)pyrazine-3-carboxylate (**7Cc**).

This coupling was performed using dichloro bis(triphenylphosphine) palladium as the catalyst and the mixture was stirred for 16 hours. Workup as in the general procedure, followed by chromatography over silica gel with hexane:ethyl acetate 3:1 followed by hexane:ethyl acetate 2:1 as eluents led to this compound as a pale yellow solid (43%), mp 82-83°; ^{1}H nmr (deuteriochloroform): δ 8.65 (d, J = 2 Hz, 1H), 8.56 (d, J = 2 Hz, 1H), 7.18 (m, 2H), 6.98 (t, J_{HH} = 9Hz, J_{HF} = 9 Hz, 1H), 4.52 (s, 2H), 4.00 (s, 3H).

Anal. Calcd. for: $C_{13}H_{10}ClFN_2O_2$; C, 55.63; H, 3.58; N, 9.98; Found: C, 55.79; H, 3.77; N, 9.59.

Nicotinic Acids **8Aa-c**, Isonicotinic Acids **8Ba-c** and Pyrazinecarboxylic Acid **8Cc**. General Procedure.

The appropriate ester **7** (0.34 mmole) was added to a solution of sodium hydroxide (1.7 mmoles) in water (0.4 ml) and methanol (0.8 ml) and the mixture was refluxed for 2 hours. The resultant solution was cooled in an ice bath, acidified with concentrated hydrochloric acid and concentrated to one-half volume by rotary evaporation. The resultant solid was collected by filtration and dried. Examination by ^1H nmr spectroscopy indicated high purity and these acids were used directly in the next step.

2-(2,5-Difluorobenzyl)nicotinic Acid (**8Aa**).

This compound was obtained as a white solid (80%), mp 145-146°; ^1H nmr (dimethyl sulfoxide-d_6): δ 8.60 (d, J = 4.8 Hz, 1H), 8.21 (d, J = 7.8 Hz, 1H), 7.39 (dd, J = 7.8 Hz, J = 4.8 Hz, 1H), 7.17 (m, 1H), 7.06 (m, 1H), 6.92 (m, 1H), 4.52 (s, 2H).

2-(2-Chloro-5-fluorobenzyl)nicotinic Acid (**8Ab**).

This compound was obtained as a white solid (78%), mp 214-215°; ^1H nmr (dimethyl sulfoxide-d_6): δ 8.60 (dd, J_{HH} = 4.8 Hz, J_{HH} = 1.8 Hz, 1H), 8.23 (dd, J_{HH} = 7.8 Hz, J_{HH} = 1.8 Hz, 1H), 7.44 (dd, J_{HH} = 8.8 Hz, J_{HF} = 5 4 Hz, 1H), 7.40 (dd, J_{HH} = 7.8 Hz, J_{HH} = 4.8 Hz, 1H), 7.10 (ddd, J_{HH} = 8.8 Hz, J_{HF} = 8.8 Hz, J_{HH} = 3.1 Hz, 1H), 6.93 (dd, J_{HF} = 9.6 Hz, J_{HH} = 3.1 Hz, 1H), 4.59 (s, 2H).

2-(2-Fluoro-5-chlorobenzyl)nicotinic Acid (**8Ac**).

This compound was obtained as a white solid (96%), mp 190-191°; ^1H nmr (dimethyl sulfoxide-d_6): δ 8.74 (dd, J_{HH} = 5.1 Hz, J_{HH} = 1.7 Hz, 1H), 8.45 (dd, J_{HH} = 7.9 Hz, J_{HH} = 1.7 Hz, 1H), 7.64 (dd, J_{HH} = 7.9 Hz, J_{HH} = 5.1 Hz, 1H), 7.32 (ddd, J_{HH} = 9.4 Hz, J_{HF} = 4.3 Hz, J_{HH} = 2.7, 1H), 7.20 (dd, J_{HH} = 9.4 Hz, J_{HF} = 9.1 Hz, 1H), 7.19 (dd, J_{HF} = 6.5 Hz, J_{HH} = 2.7 Hz, 1H), 4.62 (s, 2H).

3-(2,5-Difluorobenzyl)isonicotinic Acid (**8Ba**).

This acid was obtained as a white solid (70%), mp 253-255°; ^1H nmr (dimethyl sulfoxide-d-$_6$) δ 8.62 (d, J = 5.0 Hz, 1H), 8.56 (s, 1H), 7.69 (d, J = 5.0 Hz, 1H), 7.2 (m, 1H), 7.1 (m, 1H), 6.87 (m, 1H), 4.33 (s, 2H)

3-(2-Chloro-5-fluorobenzyl)isonicotinic Acid (**8Bb**).

This acid was obtained as a white solid (85%), mp 278-279°; ^1H nmr (dimethyl sulfoxide-d_6): δ 8.61 (d, J_{HH} = 4.9 Hz, 1H), 8.42 (s, 1H), 7.70 (d, J_{HH} 4.9 Hz, 1H), 7.50 (dd, J_{HH} = 8.8 Hz, J_{HF} = 5.3 Hz, 1H), 7.14 (ddd, J_{HH} = 8.8 Hz, J_{HF} = 8.4 Hz, J_{HH} = 3.0 Hz, 1H), 6.84 (dd, J_{HF} = 9.6 Hz, J_{HH} = 3.0 Hz, 1H), 4.39 (s, 2H)

3-(2-Fluoro-5-chlorobenzyl)isonicotinic Acid (**8Bc**).

This acid was obtained as a white solid (95%), mp 271-272°; ^1H nmr (dimethyl sulfoxide-d_6): δ 8.66 (m, 1H), 8.63 (s, 1H), 7.14 (d, J_{HH} = 4.6 Hz, 1H), 7.32 (m, 1H), 7.22 (m, 1H), 7.10 (m, 1H), 4.34 (s, 2H).

2-(2-Fluoro-5-chlorobenzyl)pyrazine-3-carboxylic Acid (**8Cc**).

This acid was obtained as a white solid (76%), mp 103-104°; ^1H nmr (deuteriochloroform): δ 11.0 (br s), 8.80 (d, J = 2 Hz, 1H), 8.50 (d, J = 2 Hz, 1H), 7.18 (m, 2H) 6.98 (t, J_{HH} = 9 Hz, J_{HF} = 9 Hz, 1H), 4.83 (s, 2H).

3-Hydroxypyrazine-2-carboxylic Acid (**10**).

The 3-aminopyrazine-2-carboxylic acid (**9**) (6.95 g, 0.05 mole) was dissolved in a mixture of water (55 ml) and sulfuric add (55 ml, 3.75 *M*) heated to 50°. A solution of sodium nitrite (18.5 ml, 0.06 mole, 3.3 *M*) was added to this solution which was cooled to 12°. The temperature was maintained at 10-16° over a 30 minute addition period and then the mixture was heated to boiling over a period of 30 minutes. After cooling to room temperature, the yellow solid was collected by filtration. The solid was dissolved in a dilute sodium bicarbonate solution, the acid reprecipitated by treatment with hydrochloric add (10%) and collected by filtration. The crude acid was recrystallized from water to yield a yellow-orange crystalline solid, 4.1 g (58%), mp 230-231° dec; lit [16] mp 223-225° dec; ^1H nmr (dimethylsulfoxide-d_6): δ 7.80 (d, J = 2 Hz, 1H), 7.65 (d, J = 2 Hz, 1H), 3.45 (br s, 1H).

Methyl 3-Hydroxypyrazine-2-carboxylate (**11**).

Dry hydrogen chloride gas was bubbled through a suspension of **11** (2.0 g, 0.014 mole) in refluxing dry methanol (40 ml) for 2.5 hours. The yellow solution was cooled to room temperature, concentrated to 15 ml by rotary evaporation and treated with ice water (10 ml). The *p*H was adjusted to 3 by addition of solid sodium bicarbonate and the mixture was continuously extracted with dichloromethane overnight. The extract was dried over magnesium sulfate and the solvent removed by rotary evaporation to give a yellow solid, 1.4 g (64%), mp 150-151°; lit [17] mp 151-152°; ^1H nmr (deuteriochloroform): δ 8.60 (d, J = 2 Hz, 1H), 8.47 (d, J = 2 Hz, 1H). 4.05 (s, 3H).

REFERENCES AND NOTES

[1] A. P. Krapcho, J. J. Landi, Jr., M. P. Hacker and J. J. McCormack, *J. Med. Chem.*, **28**, 1124 (1985).

[2] A. P. Krapcho, M. E. Petry, J. J. Landi, Jr., J. Stallman, J. F. Polsenberg, M. P. Hacker, S. Spinelli, A. Oliva, R. Di Domenico and E. Menta, *J. Heterocyclic Chem.*, **30**, 1565 (1993).

[3] A. P. Krapcho, M. E. Petry, Z. Getahun, J. J. Landi, Jr., J. Stallman, J. F. Polsenberg, C. E. Gallagher, M. E. Maresch, M. P. Hacker, F. C. Giuliani, G. Beggiolin, G. Pezzoni, E. Menta, C. Manzotti, A. Oliva, S. Spinelli and S. Tognella, *J. Med. Chem.*, **37**, 828 (1994).

[4] A. P. Krapcho, M. J. Maresch, A. L. Helgason, K. E. Rosner, M. P. Hacker, S. Spinelli, E. Menta and A. Oliva, *J. Heterocyclic Chem.*, **30**, 1597 (1993).

[5] G. W. Gribble and M. G. Saulnier, *Heterocycles*, **35**, 151 (1993).

[6] P. Knochel and R. D. Singer, *Chem. Rev.*, **93**, 2117 (1993).

[7] C. Jubert and P. Knochel, *J. Org. Chem.*, **57**, 5425 (1992).

[8] S. C. Berk, M. C. P. Yeh, N. Jeong and P. Knochel, *Organometallics*, **9**, 3053 (1990).

[9] T. Sakamoto, Y. Kondo, N. Murata and H. Yamanaka, *Tetrahedron*, **49**, 9713 (1993).

[10] E. Erdik, *Tetrahedron* **48**, 9577 (1992).

[11] Q.-Y. Chen and Y.-B. He, *Tetrahedron Letters*, **28**, 2387 (1987).

[12] E. Negishi, H. Matsushita and N. Okukado, *Tetrahedron Letters*, **22**, 2715 (1981).

[13] E. Negishi, *Acc. Chem. Res.*, **15**, 340 (1982).

[14] A. Minato, K. Tamao, K. Suzuki and M. Kumada, *Tetrahedron Letters*, **21**, 4017 (1980).

[15] E. Negishi, A. O. King and N. Okukado, *J. Org. Chem.*,

42, 1821 (1977).

[16] L. R. Fibel and P. E. Spoeri, *J. Am. Chem. Soc.*, **70**, 3911 (1948).

[17] A. Albert, D. J. Brown and H. C. S. Wood, *J. Chem. Soc.*, 2066 (1956).

[18] M. S. Newman and K. G. Ihrman, *J. Am. Chem. Soc.*, **80**, 3652 (1958).

[19] R. D. Smith and H. D. Simmons, *Org. Synth.*, **5**, 855 (1973).

[20] H. H. Fox and J. T. Gibas, *J. Org. Chem.*, **23**, 64, (1958).

[21] F. G. Mann and J. A. Reid, *J. Chem. Soc.*, 2057 (1952).

[22] K. L Shepard, S. L Graham, R. J. Hudcosky, S. R. Michelson, T. H. Scholz, H. Schwam, A. M. Smith, J. M. Sondey, K. M. Strohmaier, R. L. Smith and M. F. Sugrue, *J. Med. Chem.*, **34**, 3098 (1991).