REGIOSELECTIVE ADDITION OF GRIGNARD REAGENTS TO THE 1-PHENOXYCARBONYL SALTS OF ALKYL NICOTINATES

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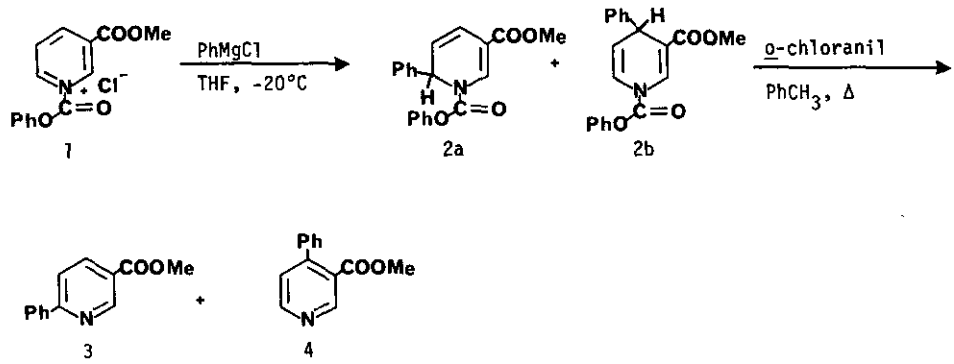
Abstract- The addition of Grignard reagents to the 1-phenoxycarbonyl salts of alkyl nicotinates affords substituted 1,2- and 1,4-dihydropyridines. The crude dihydropyridines were aromatized with o-chloranil or sulfur to give 6- and 4-substituted alkyl nicotinates. The regioselectivity of this two-step process, 6- vs. 4- substitution, was examined and found to be dependent upon the structure of the Grignard reagent. When a catalytic amount of cuprous iodide is present during the Grignard reaction, nearly exclusive 1,4-addition results. The crude 1,4-dihydropyridines were aromatized with sulfur to provide 4-substituted methyl nicotinates in moderate yield and high isomeric purity.

Recently, we have been studying the synthesis of substituted pyridines and dihydropyridines via the addition of Grignard reagents to 1-acylpyridinium salts.[1-3] The regioselectivity of this reaction, 1,2- vs. 1,4- addition, was examined and found to be dependent upon the structures of the pyridine, Grignard reagent, and the 1-acyl group, and the presence of cuprous iodide.[1,2] The 1-acylpyridinium salts are so reactive toward Grignard reagents that addition to the pyridine ring will occur in the presence of other reactive functional groups such as ketones[4], esters[1,5], and halides[2]. Since substituted 3-acylpyridines are generally difficult to prepare,[6] we decided to study the ring-alkylation of the readily available alkyl nicotinates. We report here a regioselective synthesis of 6-(or 4-) substituted alkyl nicotinates utilizing the reaction of Grignard reagents with the 1-phenoxycarbonyl salts[7] of alkyl nicotinates.

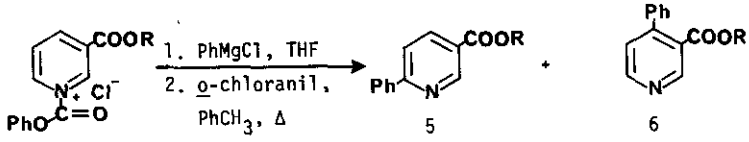
The initial reaction was performed using phenylmagnesium chloride and the phenoxycarbonyl salt of methyl nicotinate(1) in tetrahydrofuran (THF). The crude dihydropyridine mixture 2 was aromatized with o-chloranil[8] to give methyl 6-phenylnicotinate(3) and methyl 4-phenylnicotinate(4) in a ratio of 4:1 (see Scheme I).

Scheme I



To determine what effect the structure of the ester function has on the regioselectivity, the analogous reactions using i-propyl nicotinate and t-butyl nicotinate were performed. The results are given in Table I. Interestingly, the structure of the ester has little effect on the regiochemistry.

TABLE I

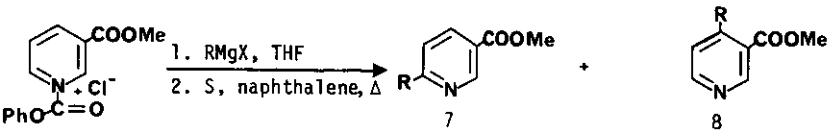


R[a]	Ratio[b] 5/6	Overall Yield,%[c] of 5	mp, °C of 5
Me	79/21	58	113-114
i-Pr	87/13	60	68-69
t-Bu	83/17	57	78-79

[a]Reactions were performed on a 3-mmol scale in THF. [b]The ratio was determined by ^{1}H NMR. [c]Yields are for isolated, pure, material obtained from radial preparative layer chromatography (silica gel, ethyl acetate-hexanes).

The effect of the Grignard reagent on the regioselectivity was studied and the results are given in Table II. The crude dihydropyridines were aromatized with sulfur[9] in refluxing naphthalene, and the ratio of aromatized products (7 and 8) was determined by GC analysis of the crude material. The 6-substituted methyl nicotinates 7 were isolated in low yield by chromatography on silica gel. With methyl and n-butyl Grignard reagents, a 60/40 mixture of 4- and 6-substituted nicotinates resulted. Cyclohexylmagnesium chloride gave mainly 1,4-addition, presumably due to a steric effect.[1] The ratio was reversed with phenylmagnesium chloride, giving mainly the 6-substituted product. The preferential attack of aryl Grignard reagents at the α-position of other 1-acylpyridinium salts has been reported.[1,10]

TABLE II



R[a]	Ratio[b] 7/8	Crude Yield,% of 7+8	Purified Yield[c] of 7
Me	40/60	20	5
n-Bu	43/57	83	29
Cyclohexyl	16/84	65	4
Phenyl	84/16	76	30(58)[d]

[a]Reactions were performed on a 3-mmol scale. [b]The ratio was determined by GC. [c]Yields are for isolated, pure, material obtained from radial preparative layer chromatography. [d]Yield when o-chloranil was used for the aromatization. See Table I.

Synthesis of Methyl 4-Alkylnicotinates. We recently reported that a catalytic amount (5 mol %) of CuI has a major effect on the regioselectivity of the Grignard reaction with 1-acylpyridinium salts, causing nearly exclusive attack at the 4-position of the pyridine ring. Subsequent aromatization of the crude 1,4-dihydropyridines provides 4-substituted pyridines in good yield.[1,2] We have studied the effect of CuI (5 mol %) on the reaction of Grignard reagents with the 1-phenoxycarbonyl salt of methyl nicotinate (1), and the results are given in Table III. The Grignard reagent was added dropwise to a solution of methyl nicotinate, CuI (5%), and phenyl chloroformate in THF-methyl sulfide (3 equiv) at -20°C to give 1,4-dihydropyridines 9a (see Scheme II). The reaction is regiospecific, forming only minor amounts of the isomeric 1,2-dihydropyridines 9b. Aromatization of the crude dihydropyridines 9 with sulfur in refluxing decalin gave methyl 4-alkylnicotinates 8 in moderate to good yield.

Scheme II

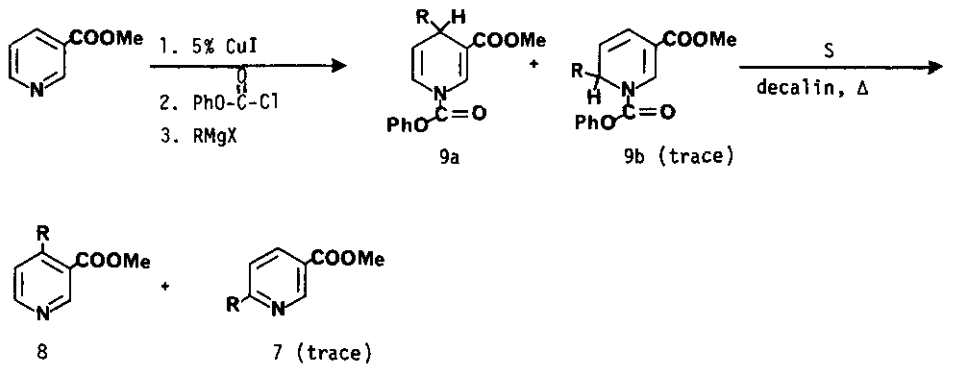


TABLE III. Synthesis of Methyl 4-Alkylnicotinates (See Scheme II)

R[a]	Ratio[b] 8/7	Crude Yield,% of 7+8	Purified Yield,%[c] of 8
Me	99/1	58	48
n-Bu	93/7	52	44
Cyclohexyl	96/4	49	41
Phenyl	95/5	64	60

[a]Reactions were performed on a 3-mmol scale. [b]The ratio was determined by GC. [c]Yields are for isolated, pure, material obtained from radial preparative layer chromatography.

EXPERIMENTAL SECTION

Reactions involving organometallic reagents were performed in oven-dried glassware under a N_2 atmosphere. Tetrahydrofuran (THF) was dried by distillation from sodium benzophenone ketyl prior to use. Toluene was dried over 3A molecular sieves. Cuprous iodide (CuI), ultrapure, was obtained from Alfa Products. Other solvents and reagents from commercial sources were generally used without further purification.

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on a Varian EM-360 spectrometer. Gas-liquid chromatography (GC) was performed with a Hewlett-Packard 5830A gas chromatograph equipped with a 30 m x 0.25 mm FSOT column packed with OV-101.

Methyl 6-Phenylnicotinate (3). A solution of methyl nicotinate (411 mg, 3 mmol) in 6 ml of dry THF under N_2 was cooled to -20°C (dry ice/CCl_4). Phenyl chloroformate (0.39 ml, 3.0 mmol) was added dropwise and the mixture was stirred at -20°C for 10 min. A solution of phenylmagnesium chloride (3.0 mmol) in 1.5 ml of THF was added dropwise. The mixture was stirred at -20°C for 15 min followed by the addition of aqueous 20% NH_4Cl solution (20 ml). Ether (50 ml) was added and the organic layer was washed with 20-ml portions of 10% HCl (2X), water, and brine. After drying ($MgSO_4$), the solution was concentrated to give the crude dihydropyridine as a viscous oil. To this oil in dry toluene (20 ml) was added 810 mg (3.3 mmol) of o-chloranil. The mixture was heated at reflux for 3 h and cooled to room temperature. Ether (50 ml) and 25 ml of 1N NaOH were added, and after stirring for 10 min the mixture was filtered through celite. The organic layer was washed with 20-ml portions of water and brine. After drying ($MgSO_4$), the solution was filtered and concentrated to yield 875 mg of a yellow solid. Purification by radial preparative layer chromatography (0.1% MeOH/CH_2Cl_2) gave 370 mg (58%) of methyl 6-phenylnicotinate (3) as a white solid. The product was recrystallized from ethyl acetate to give an analytical sample of 3: mp 113-114°C; NMR ($CDCl_3$) δ9.4 (bs,1H), 8.44 (d of d,1H,J=2,8

Hz), 8.18 (m,2H), 7.86 (d,1H,J=8 Hz), 7.52 (m,3H), 4.0 (s,3H); IR (KBr) 1720, 1600, 1290 cm^{-1}. Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.23; H, 5.19; N, 6.57. Found: C, 73.13; H, 5.30; N, 6.52.

Isopropyl 6-Phenylnicotinate. Prepared from isopropyl nicotinate using the procedure described above: 60% yield; mp 68-69°C (hexane); NMR (CCl_4 δ9.3 (bs,1H), 7.2-8.6 (bm,7H), 5.3 (q,1H), 1.4 (d,6H)); IR (KBr) 1710, 1600, 1290 cm^{-1}. Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.26; N, 5.80. Found: C, 74.57; H, 6.11; N, 5.87.

tert-Butyl 6-Phenylnicotinate. Prepared from tert-butyl nicotinate using the procedure described above: 57% yield; mp 78-79°C (hexane); NMR (CCl_4) δ9.25 (bs,1H), 7.2-8.4 (bm,7H), 1.6 (s,9H); IR (KBr) 1710, 1600, 1300 cm^{-1}. Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.48. Found: C, 75.05; H, 6.78; N, 5.51.

Synthesis of Methyl 6-Alkylnicotinates. General Procedure. The crude dihydropyridines were prepared from methyl nicotinate (3 mmol) and Grignard reagents using the procedure described above for the synthesis of 3. The dihydropyridines were treated with sublimed sulfur (3 mmol) in refluxing naphthalene (10 g) for 3 h under N_2. Ether (50 ml) was added to the cooled reaction mixture followed by extraction with four 30-ml portions of cold 10% HCl. Methylene chloride (50 ml) was added to the cooled acid extract. The mixture was made basic with 10% NaOH and extracted with CH_2Cl_2. The combined organic layer was dried (K_2CO_3), filtered, and concentrated to give the crude substituted nicotinates. The ratio of methyl 6- and 4-alkylnicotinates was determined by GC analysis (see Table II). The 6-substituted methyl nicotinates 7 were isolated pure by radial preparative layer chromatography (silica gel, EtOAc-hexane).

Methyl 6-n-Butylnicotinate: Isolated as a clear oil: 29% yield; NMR ($CDCl_3$) δ9.25 (bs,1H), 8.3 (d of d,1H,J=2,8 Hz), 7.3 (d,1H,J=8 Hz), 4.0 (s,3H), 2.9 (t,2H), 0.7-2.0 (bm,7H); IR (neat) 1725, 1600, 1300 cm^{-1}. Anal. Calcd for $C_{10}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.32; H, 7.89; N, 7.29.

Methyl 6-Cyclohexylnicotinate. Isolated as a clear oil: 4.2% yield; NMR ($CDCl_3$) δ9.25 (bs,1H), 8.3 (d of d,1H,J=2,8 Hz), 7.3 (d,1H,J=8 Hz), 4.0 (s,3H), 2.8 (bs,1H), 1.1-2.3 (bm,10H). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.52; N, 6.39. Found: C, 71.36; H, 7.74; N, 6.44.

Synthesis of Methyl 4-Alkylnicotinates 8. General Procedure. A solution of methyl nicotinate (411 mg, 3 mmol), 30 mg of CuI, and 1.5 ml of methyl sulfide in 8 ml of dry THF was cooled to -20°C (dry ice/CCl_4). Phenyl chloroformate (0.39 ml, 3.0 mmol) was added dropwise and the

mixture was stirred at -20°C for 10 min. A solution of the Grignard reagent (3.0 mmol) in 2.0 ml of THF was added dropwise. The mixture was stirred at -20°C for 15 min, allowed to come to room temperature, and quenched with 20 ml of aqueous 20% NH_4Cl solution. Ether (50 ml) was added and the organic layer was washed with 20 ml portions of 20% NH_4Cl/NH_4OH (50:50), water, 10% HCl (2X), water, and brine. After drying ($MgSO_4$), the solution was concentrated to give the crude dihydropyridine 9 as a viscous oil. The dihydropyridines were aromatized with sulfur (3 mmol) in refluxing decalin (3h). Isolation and purification were the same as described above for the synthesis of methyl 6-alkylnicotinates.

Methyl 4-Methylnicotinate: Isolated as a clear oil: 48% yield; NMR ($CDCl_3$) δ9.25 (s,1H), 8.68 (d,1H,J=6 Hz), 7.28 (d,1H,J=6 Hz), 4.0 (S,3H), 2.65 (s,3H); IR (neat) 1720, 160 , 1440 cm^{-1}. Anal. Calcd for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.47; H, 6.14; N, 9.06.

Methyl 4-n-Butylylnicotinate: Isolated as a clear oil: 44% yield; NMR ($CDCl_3$) δ9.2 (s,1H), 8.7 (d,1H,J=6 Hz), 7.28 (d,1H,J=6 Hz), 4.0 (s,3H), 3.05 (t,2H), 0.8-1.9 (bm,7H); IR (neat) 1720, 1590, 1280 cm^{-1}. Anal. Calcd for $C_{10}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.34; H, 7.84; N, 7.27.

Methyl 4-Cyclohexylnicotinate: Isolated as a clear oil: 41% yield; NMR ($CDCl_3$) δ9.1 (s,1H), 8.72 (d,1H,J=6 Hz), 7.4 (d,1H,J=6 Hz), 4.0 (s,3H), 3.5 (bs, 1H), 1.1-2.2 (bm,10H); IR (neat) 1720, 1590, 1280 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.82; N, 6.39. Found: C, 71.15; H, 7.69; N, 6.36.

Methyl 4-Phenylnicotinate: Isolated as a clear oil: 60% yield; NMR ($CDCl_3$) δ9.18 (s,1H), 8.82 (d,1H,J=5 Hz), 7.48 (s,5H), 7.35 (d,1H), 3.7 (s,3H); IR (neat) 1720, 1580, 1280 cm^{-1}. Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.23; H, 5.20; N, 6.57. Found: C, 73.47; H, 5.17; N, 6.52.

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