Synthesis of Alkyl 2-Phenylnicotinates

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Various alkyl 6-ethoxy-2-phenyl-5,6-dihydro-4*H*-pyran-3-carboxylate **2A** are easily converted to the corresponding nicotinates **3** by reaction with hydroxylamine hydrochloride in refluxing absolute ethanol.

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It is well known that pyridine derivatives are synthesized from other heterocyclic compounds, such as furans, isoxazoles and pyrones, having proper substituents [1]. The α-alkoxypyrans have been reported to be transformed into pyridine derivatives by treatment with ammonia [2] or hydroxylamine hydrochloride [3]. In the previous paper [4], we reported that the reaction of 3-acyl-6-ethoxy-5,6-dihydro-4*H*-pyrans and hydroxylamine hydrochloride gave 4-cyanoethylisoxazoles whose substituents at the 3 and 5 positions were transformed from substituent at the 2 position and the acyl group of the dihydropyrans. Different heterocyclic compounds were synthesized from anologous α-alkoxydihydropyrans, which was of interest. In order to clarify if the selectivity changes are observed by replacing the C3 acyl group of the 3-acyldihydropyrans with ester group, we carried out the reactions of alkyl 6-ethoxy-2-phenyl-5,6-dihydro-4*H*-pyran-3-carboxylates **2A**.

The starting material, alkyl 2-benzoylacrylates **1**, to prepare the dihydropyrans was obtained from alkyl benzoylacetates by the method previously developed in our laboratory [5]. The alkyl 6-ethoxy-2-phenyl-5,6-dihydro-4*H*-pyran-3-carboxylates **2A** were synthesized in good yields from the hetero Diels-Alder reaction [6] of **1** with ethyl vinyl ether as previously described procedure [7]. Regioselectivity of the reaction was completely achieved in all acrylates (Table 1). The ir spectra of the product showed conjugated ester group at *ca.* 1690 cm^{-1}. In the ^1H nmr spectra of **2Aa-d** the signal of the phenyl group appeared as broad singlet at *ca.* 7.3 ppm. If the products were regioisomer **2B** the phenyl proton *ortho* to the carbonyl group should show the signal at considerably downfield

Table 1

Alkyl 6-Ethoxy-2-phenyl-5,6-dihydro-4*H*-pyran-3-carboxylate **2A**

Entry	R	Yield (%) [a]
a	CH_3	87
b [b]	CH_3CH_2	99
c	$(CH_3)_2CH$	93
d	$PhCH_2$	82
e	cyclohexyl	78
f	8-phenylmenthyl	95

[a] Isolated yields. [b] Reference 7.

[4]. The aromatic protons of **2Ae** and **2Af** shows somewhat complex pattern due to additional phenyl group but no signals below 7.6 ppm. The product **2Af** prepared from (1'*R*,2'*S*,5'*R*)-5-methyl-2-(1-methyl-1-phenylethyl)-cyclohexyl 2-benzoylacrylate **1f** [8] should be a mixture of deastereoisomers with respect to C6 ethoxy group. However the C6 proton was observed as a triplet presumably due to no influence of the chiral ester group.

The alkyl 6-ethoxy-2-phenyl-5,6-dihydro-4*H*-pyran-3-carboxylates **2A** were refluxed with 1.2 equivalents of hydroxylamine hydrochloride in absolute ethanol. Among

Table 2

Alkyl 2-Phenylnicotinates **3**

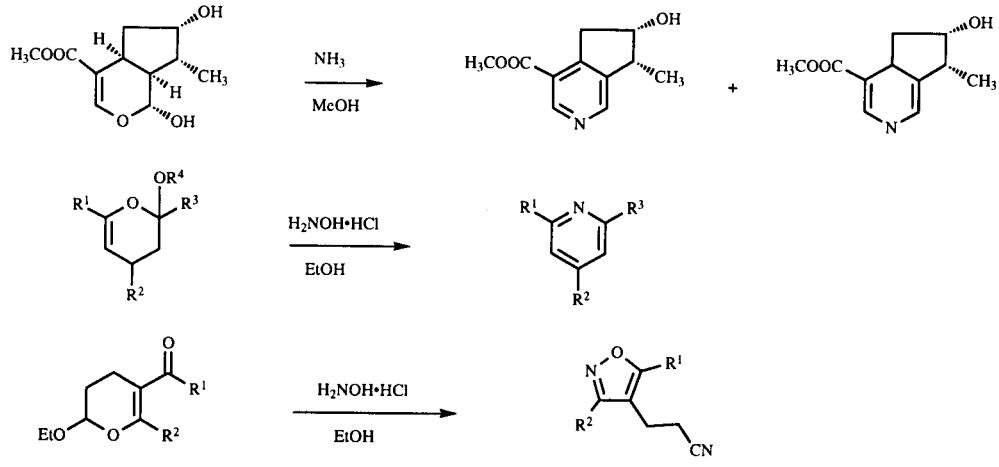
Entry	R	Yield (%) [a]
a	CH_3	51
b [b]	CH_3CH_2	70
c	$(CH_3)_2CH$	50
d	$PhCH_2$	48
e	cyclohexyl	43
f	8-phenylmenthyl	32

[a] Isolated yields.

the complex products only alkyl 2-phenylnicotinates **3** but not isoxazole derivatives were isolated in moderate yields (Table 2). The reaction with 2 equivalents of hydroxylamine hydrochloride did not change the yields of the products **3**. In the ^1H nmr spectra of **3a-e** the characteristic three double doublets at *ca.* 7.3, 8.1 and 8.8 ppm were assigned to the C5, C4 and C6 of the pyridine ring respectively. The signals of the C5 and C4 protons of **3f** appeared at considerable downfield shift compared with the other. This suggests that the phenyl group of the substituents have some interaction, such as π-stacking [9], with the pyridine ring. If the conversion of pyridine ring of **3f** into the corresponding dihydropyridine was achieved we will obtain an ideal NADH type compound [10] in hand. Thus we carried out the known sequential reaction [11] (*N*-alkylation and then reduction) to **3f** but unfortunately the conversion of pyridine ring into dihydropyridine ring was not successful.

In conclusion, alkyl nicotinates **3** were obtained from the reaction of hydroxylamine hydrochloride and alkyl 6-

Chart 1



ethoxy-2-phenyl-5,6-dihydro-4*H*-pyran-3-carboxylates **2A**, in which an ester group was substituted for the acyl group of 3-acyl-6-ethoxy-5,6-dihydro-4*H*-pyrans, which gave 4-cyanoethylisoxazoles under the same reaction condition [4]. Further investigations to clarigy the reaction mechanism are now in progress.

Chart 2

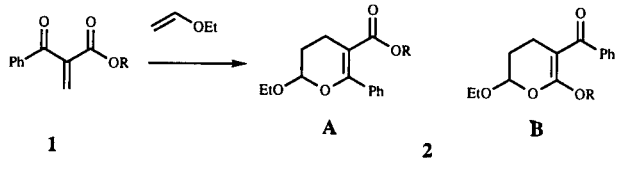


Chart 3

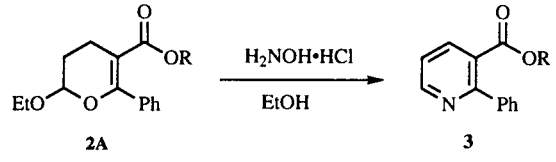
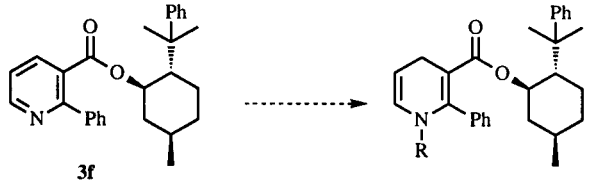


Chart 4



EXPERIMENTAL

Melting points were measured on a Yanako micro-melting point apparatus and are uncorrected. Extracts were dried over anhydrous magnesium sulfate. The ir spectra of solids (potassium bromide) and liquids (film) were recorded on a JASCO-IR-810 spectrophotometer. Mass spectra were observed on a JEOL JMS-DX300 instrument. The nmr spectra were obtained with JEOL JMN-EX 270 spectrometer in deuteriochloroform with tetramethylsilane as the internal reference. Column chromatography was carried out on silica gel, 100~200 mesh, Micro Bead 4B, Fuji-Davison Chemical LTD.

Alkyl 6-Ethoxy-2-phenyl-5,6-dihydro-4*H*-pyran-3-carboxylates.

In addition to the compounds described in ref 7 the following compounds were synthesized and isolated.

Methyl 6-Ethoxy-2-phenyl-5,6-dihydro-4*H*-pyran-3-carboxylate **2Aa**.

This compound was obtained as a viscous oil; ir: ν 1690, 1635, 1600, 760, 700; ^{1}H nmr: δ 1.26 (3H, t, J = 6.9 Hz, CH_3), 1.80-2.05 (2H, m, 5-CH_2), 2.50-2.56 (2H, m, 4-CH_2), 3.48 (3H, s, CH_3), 3.83 (2H, qABq, J = 9.4, 6.9 Hz, OCH_2), 5.22 (1H, dd, J = 3.9, 2.5 Hz, 6-H), 7.35 (5H, br s, ArH); ^{13}C nmr: δ 15.1, 18.6, 26.1, 51.0, 64.3, 98.2, 104.1, 127.7, 128.4, 128.9, 136.9, 160.0, 168.7.

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.70; H, 6.72.

Isopropyl 6-Ethoxy-2-phenyl-5,6-dihydro-4*H*-pyran-3-carboxylate **2Ac**.

This compound was obtained as a viscous oil; ir: ν 1690, 1640, 1600, 760, 700; ^{1}H nmr: δ 0.93 (3H, d, J = 6.4 Hz, CH_3), 0.94 (3H, d, J = 6.4 Hz, CH_3), 1.26 (3H, t, J = 6.9 Hz, CH_3), 1.83-2.05 (2H, m, 5-CH_2), 2.40-2.55 (2H, m, 4-CH_2), 3.83 (2H, qABq, J = 9.4, 6.9 Hz, OCH_2), 4.82 (1H, heptet, J = 6.4 Hz, OCH), 5.21 (1H, dd, J = 4.0, 3.0 Hz, 6-H), 7.33 (5H, br s, ArH); ^{13}C nmr: δ 15.2, 18.6, 21.4, 21.5, 26.1, 64.3, 67.1, 98.3, 104.9, 127.7, 128.55, 128.63, 137.3, 159.4, 167.8.

Anal. Calcd. for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: 70.23; H, 7.51.

Benzyl 6-Ethoxy-2-phenyl-5,6-dihydro-4*H*-pyran-3-carboxylate **2Ad**.

This compound was obtained as colorless crystals; mp 86° (from benzene-hexane); ir: ν 1680, 1640, 1600, 770, 760, 700; ^{1}H nmr: δ 1.26 (3H, t, J = 6.9 Hz, CH_3), 1.83-2.05 (2H, m, 5-CH_2), 2.50-2.60 (2H, m, 4-CH_2), 3.82 (2H, qABq, J = 9.4, 6.9

Hz, OCH_2), 4.95 (2H, s, OCH_2Ph), 5.21 (1H, dd, J = 4.0, 2.5 Hz, 6-H), 6.93-6.99 (2H, m, ArH), 7.10-7.51 (8H, m, ArH); ^{13}C nmr: δ 15.1, 18.7, 26.1, 64.3, 65.8, 98.4, 104.2, 127.7, 127.8, 127.9, 128.2, 128.5, 128.9, 136.0, 137.0, 160.2, 168.1.

Anal. Calcd. for $C_{21}H_{22}O_4$: C, 74.54; H, 6.55. Found: 74.32; H, 6.53.

Cyclohexyl 6-Ethoxy-2-phenyl-5,6-dihydro-4*H*-pyran-3-carboxylate **2Ae**.

This compound was obtained as a viscous oil; ir: ν 1690, 1640, 1600, 760, 700; ^1H nmr: δ 1.07-1.30 (5H, m), 1.27 (3H, t, J = 7.0 Hz, CH_3), 1.40-1.68 (5H, m), 1.88-2.03 (2H, m, 5-CH_2), 2.50-2.56 (2H, m, 4-CH_2), 3.83 (2H, qABq, J = 9.4, 7.0 Hz, OCH_2), 4.62 (1H, m, OCH), 5.21 (1H, dd, J = 4.0, 2.5 Hz, 6-H), 7.33 (5H, br s, ArH).

Anal. Calcd. for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: 72.84; H, 7.77.

(1'*R*,2'*S*,5'*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl 6-Ethoxy-2-phenyl-5,6-dihydro-4*H*-pyran-3-carboxylate **2Af**.

This compound was obtained as a viscous oil; ir: ν 1680, 1630, 1600, 760, 700; ^1H nmr: δ 0.79 (3H, d, J = 6.9 Hz, CH_3), 1.16 (3H, s, CH_3), 1.22 (3H, s, CH_3), 1.24 (3H, t, J = 6.9 Hz, CH_3), 3.80 (2H, qABq, J = 9.9, 6.9 Hz, OCH_2), 4.72 (1H, dt J = 10.5, 4.5 Hz, OCH), 5.18 (1H, t, J = 3.0 Hz, 6-H), 7.05-7.50 (10H, m, ArH); ^{13}C nmr: δ 15.1, 17.2, 21.7, 21.8, 25.9, 26.4, 26.8, 31.2, 34.6, 39.8, 41.5, 50.4, 64.0, 73.8, 97.5, 105.2, 124.8, 125.5, 127.6, 127.8, 128.7, 128.8, 137.2, 151.7, 159.6, 166.8.

Anal. Calcd. for $C_{30}H_{38}O_4$: C, 77.89; H, 8.28. Found: 78.19; H, 8.21.

Reaction of 3,4-Dihydropyrans with Hydroxylamine Hydrochloride. General Procedure.

A mixture of dihydropyran **2A** (1 mmole) and hydroxylamine hydrochloride (82 mg, 1.2 mmoles) in absolute ethanol (10 ml) was refluxed for 5 hours. The solvent was evaporated *in vacuo* and water (10 ml) was added to the residue. The organic phase was separated and extracted with ether. The ether layer was washed with brine, dried and evaporated. The resulting residue was subjected to column chromatography to give the products.

Methyl 2-Phenylnicotinate **3a**.

This compound was obtained as a viscous oil; ir: ν 1725, 1580, 1560; ^1H nmr: δ 3.70 (3H, s, CH_3), 7.34 (1H, dd, J = 8.1, 4.8 Hz, 5-H), 7.42-7.47 (3H, m, ArH), 7.52-7.57 (2H, m, ArH), 8.10 (1H, dd, J = 8.1, 1.8 Hz, 4-H), 8.78 (1H, dd, J = 4.8, 1.8 Hz, 6-H); ms: m/z 213 (M^+, 16), 198 (100), 182 (18), 154 (19), 127 (21), 77 (21).

Anal. Calcd. for $C_{13}H_{11}O_2N$: C, 73.23; H, 5.20; N, 6.57. Found: C, 72.90; H, 5.48; N, 6.32.

Ethyl 2-Phenylnicotinate **3b**.

This compound was obtained as a viscous oil; ir: ν 1720, 1580, 1560; ^1H nmr: δ 1.04 (3H, t, J = 7.3 Hz, CH_3), 4.14 (2H, q, J = 7.3 Hz, OCH_2), 7.34 (1H, dd, J = 7.7, 4.8 Hz, 5-H), 7.40-7.44 (3H, m, ArH), 7.50-7.54 (2H, m, ArH), 8.10 (1H, dd, J = 7.7, 1.8 Hz, 4-H), 8.76 (1H, dd, J = 4.8, 1.8 Hz, 6-H); ms: m/z 227 (M^+, 18), 198 (100), 182 (23), 154 (19), 127 (18), 77 (13).

Anal. Calcd. for $C_{14}H_{13}O_2N$: C, 73.99; H, 5.77; N, 6.16. Found: 73.86; H, 6.03; N, 5.90.

Isopropyl 2-Phenylnicotinate **3c**.

This compound was obtained as a viscous oil; ir: ν 1720, 1580, 1560; ^1H nmr: δ 1.06 (6H, d, J = 6.2 Hz, CH_3), 5.03 (1H, heptet, OCH), 7.34 (1H, dd, J = 7.7, 4.8 Hz, 5-H), 7.40-7.49 (3H, m, ArH), 7.50-7.55 (2H, m, ArH), 8.09 (1H, dd, J = 7.7, 1.8 Hz, 4-H), 8.76 (1H, dd, J = 4.8, 1.8 Hz, 6-H); ms: m/z 241 (M^+, 20), 198 (100), 182 (27), 155 (28), 127 (19), 77 (12).

Anal. Calcd. for $C_{15}H_{15}O_2N$: C, 74.67; H, 6.27; N, 5.80. Found: 74.40; H, 6.36; N, 5.60.

Benzyl 2-Phenylnicotinate **3d**.

This compound was obtained as a viscous oil; ir: ν 1725, 1580, 1560; ^1H nmr: δ 5.13 (2H, s, OCH_2), 7.02 (1H, dd, J = 7.2, 3.5 Hz, ArH), 7.20-7.30 (4H, m, ArH), 7.33 (1H, dd, J = 8.1, 4.8 Hz, 5-H), 7.35-7.54 (5H, m, ArH), 8.11 (1H, dd, J = 8.1, 1.8 Hz, 4-H), 8.77 (1H, dd, J = 4.8, 1.8 Hz, 6-H); ms: m/z 289 (M^+, 22), 198 (77), 183 (47), 155 (35), 127 (18), 91 (100).

Anal. Calcd. for $C_{19}H_{15}O_2N$: C, 78.87; H, 5.23; N, 4.84. Found: 78.54; H, 5.45; N, 4.58.

Cyclohexyl 2-Phenylnicotinate **3e**.

This compound was obtained as a viscous oil; ir: ν 1725, 1580, 1560; ^1H nmr: δ 1.16-1.70 (10H, m, CH_2 x 5), 4.82 (1H, m, OCH), 7.33 (1H, dd, J = 7.7, 4.8 Hz, 5-H), 7.39-7.47 (3H, m, ArH), 7.50-7.56 (2H, m, ArH), 8.09 (1H, dd, J = 7.7, 1.8 Hz, 4-H), 8.76 (1H, dd, J = 4.8, 1.8 Hz, 6-H); ms: m/z 281 (M^+, 28), 199 (100), 182 (59), 154 (61), 127 (29), 55 (37).

Anal. Calcd. for $C_{18}H_{19}O_2N$: C, 76.84; H, 6.81; N, 4.98. Found: 76.37; H, 6.79; N, 5.03.

(1'*R*,2'*S*,5'*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl 2-Phenylnicotinate **3f**.

This compound was obtained as a viscous oil; ir: ν 1705, 1585, 1560; ^1H nmr: δ 0.62 (1H, q, J = 11.0 Hz, 6'a-H), 0.78 (1H, qd J = 12.9, 3.3 Hz, 4'a-H), 0.83 (3H, d, J = 6.6 Hz, CH_3), 1.05 (1H, qd, J = 12.9, 3.0 Hz, 3'a-H), 1.14 (3H, s, CH_3), 1.21 (3H, s, CH_3), 1.20-1.49 (1H, m, 5'a-H), 1.55-1.90 (3H, m, 3'e-, 4'e-, 6'e-H), 1.87 (1H, td, J = 11.0, 3.6 Hz, 2'a-H), 4.89 (1H, td, J = 11.0, 4.3 Hz, 1'a-H), 6.80-7.20 (5H, m, ArH), 7.17 (1H, dd, J = 7.9, 5.0 Hz, 5-H), 7.39 (5H, br s, ArH), 7.54 (1H, dd, J = 7.9, 1.6 Hz, 4-H), 8.67 (1H, dd, J = 5.0, 1.6 Hz, 6-H); ^{13}C nmr: δ 21.8, 24.7, 26.5, 28.2, 31.2, 34.4, 39.5, 41.0, 50.1, 75.7, 121.3, 124.8, 125.1, 127.1, 127.85, 127.89, 128.3, 128.8, 138.1, 140.4, 150.7, 151.4, 159.3, 166.4; $[\alpha]_D^{25}$ -95.5° (c, 0.02, chloroform).

Anal. Calcd. for $C_{28}H_{31}O_2N$: C, 81.32; H, 7.56; N, 3.39. Found: 81.12; H, 7.37; N, 3.23.

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