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SYNTHESIS AND MESOMORPHIC PROPERTIES OF A SERIES OF PHENYL 6-(4-ALKOXYPHENYL)NICOTINATES

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Abstract — A new homologous series of phenyl 6-(4-alkoxyphenyl)nicotinates (nOPNicP, n=3-7) was synthesized. The entire synthetic procedure was completed in a short two-step process. Very good two-step overall yields of 70-80% were obtained and high α–regioselective addition of Grignard reagents to 1-acylnicotinium salts was observed while preparing this series of liquid crystals. Spectral analyses were in accordance with the expected structures. Their thermotropic behaviours were studied using polarizing optical microscopy and further confirmed by differential scanning calorimetry. Smectic A phase was found to be the only mesophase in this series of compounds.

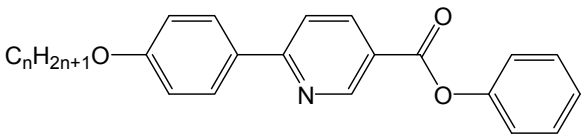
INTRODUCTION

Advances in the fields such as the applications, the physics, or the theory of liquid crystals depend very critically upon the organic chemist and his role in synthesizing materials. In studying the effect of molecular structure on liquid crystalline properties, it is often profitable to examine the effects of making relatively small changes in the molecular structure of one particular type of liquid crystalline compound, i.e., retaining the greater part of the molecular skeleton unaltered.[1]

Although a plethora of pyridine containing liquid crystalline compounds were synthesized before,[2-6] only one Japanese patent concerning nicotine containing liquid crystalline compounds was reported.[7] Compounds in the subject patent were claimed to be capable of exhibiting a nematic liquid crystal phase and useful as a liquid crystal composition for display elements.

Previously, we prepared various 2- or 4-substituted pyridines and alkaloids by regioselective addition of an organometallic reagent to 1-acylpyridinium salts.[8] Recently, we successfully applied this methodology to prepare some pyridine or quinoline containing liquid crystalline compounds.[9] In this paper, we report a facile and efficient synthesis of a homologous series of liquid crystalline phenyl

6-(4-alkoxyphenyl)nicotinates (nOPNicP, =3-7) and their mesomorphic studies using differential scanning calorimetry (DSC) and polarized optical microscopy (POM), respectively. The structure of the target material is as follows:

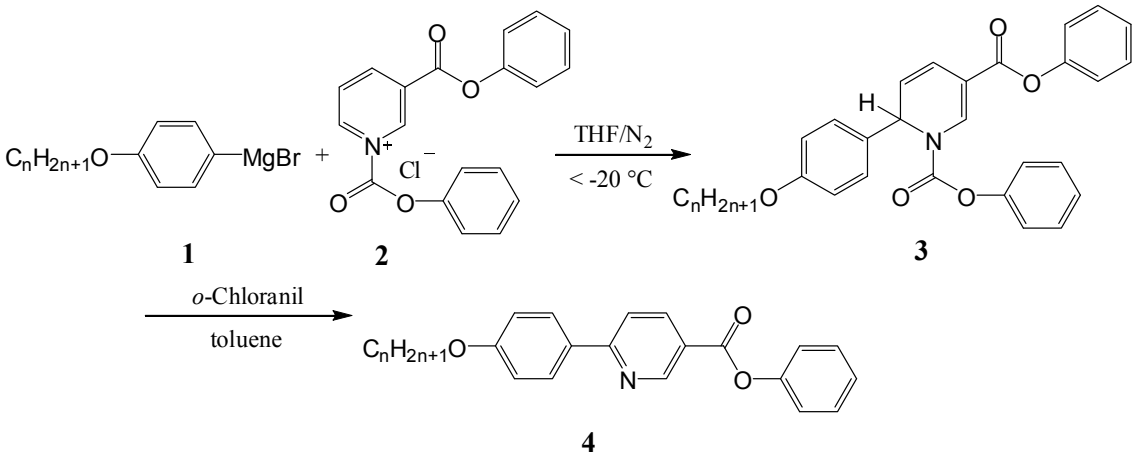


nOPNicP, n=3-7

RESULTS AND DISCUSSION

Synthesis of the phenyl 6-(4-alkoxyphenyl)nicotinates (nOPNicP, n=3-7)

The syntheses of the phenyl 6-(4-alkoxyphenyl)nicotinates (nOPNicP, n=3-7) were carried out in a short two-step reaction as outlined in Scheme 1.



Scheme 1

First, the Grignard reagents of 4-alkoxyphenylmagnesium bromides (prepared from bromoalkanes and 4-bromophenol) **1** were allowed to react with phenyl *N*-phenyloxycarbonylnicotinium chloride **2** to afford a 1,2-dihydronicotinate adducts **3**. Then, the 1,2-adducts were oxidized by *o*-chloranil to afford the desired products, phenyl 6-(4-alkoxyphenyl)nicotinates (nOPNicP, n = 3-7) **4**. Yields of **4** were found to be excellent in a range of 70-79% (Table 1). This is a valuable approach to synthesizing the phenyl 6-(4-alkoxyphenyl)nicotinates, in which an ester functional group was already built-in in reactant. It is known that nucleophilic attacking of a Grignard reagent and its regioselectivity on pyridine ring can be greatly enhanced by phenyl chloroformate.[10] Apparently phenyl choloroformate was successfully used in this experiment not only to enhance the reactivity of pyridine ring but also to prevent the ester group on the pyridine from being attacked by the Grignard reagent.

Table 1. Yields of phenyl 6-(4-alkoxyphenyl)nicotinates (nOPNicP, n = 3-7)

Entry (n)	Alkyl	Yield[a](%)
4a (n=3)	propyl	71
4b (n=4)	butyl	75
4c (n=5)	pentyl	79
4d (n=6)	hexyl	75
4e (n=7)	heptyl	70

[a]Isolated yields by column chromatography (methylene chloride/hexane) on silica gel.

α-Regioselectivity of Grignard reagent attacking on the pyridine ring was found to be overwhelmingly dominant by this synthetic methodology. Trace amounts of γ-addition product can be easily separated from those major α-addition product using simple liquid chromatography (hexane: methylene choloride = 1: 2.5) due to a high polarity difference in these two compounds.

Thermotropic behaviour of phenyl 6-(4-alkoxyphenyl)nicotinates

Mesophase transition temperatures and their corresponding transition enthalpies were determined by differential scanning calorimetry (DSC) with heating and cooling rates of 5 ºC min^{-1} (Table 2). Generally, even numbers of alkyl chains provide higher isotropic-to-smectic A phase transition temperatures than those odd-number homologues in the series of nOPNicP compounds. The enthalpies of fusion of phenyl 6-(4-alkoxyphenyl)nicotinates are rather high around 30 KJ mol^{-1}, which could limit the usefulness of these compounds in forming eutectic mixtures of low melting point.[11] The smectic A-to-isotropic transition enthalpies found in the series of nOPNicP compounds are typically in the range of 4 to 6 KJ mol^{-1}.

Table 2. Phase transition temperatures (ºC) and corresponding transition enthalpies (KJ mol^{-1}), in parentheses, for homologous series of nOPNicP, n = 3-7 were determined by the second scans at a heating and cooling rate of 5 ºC min^{-1} from differential scanning calorimetry.

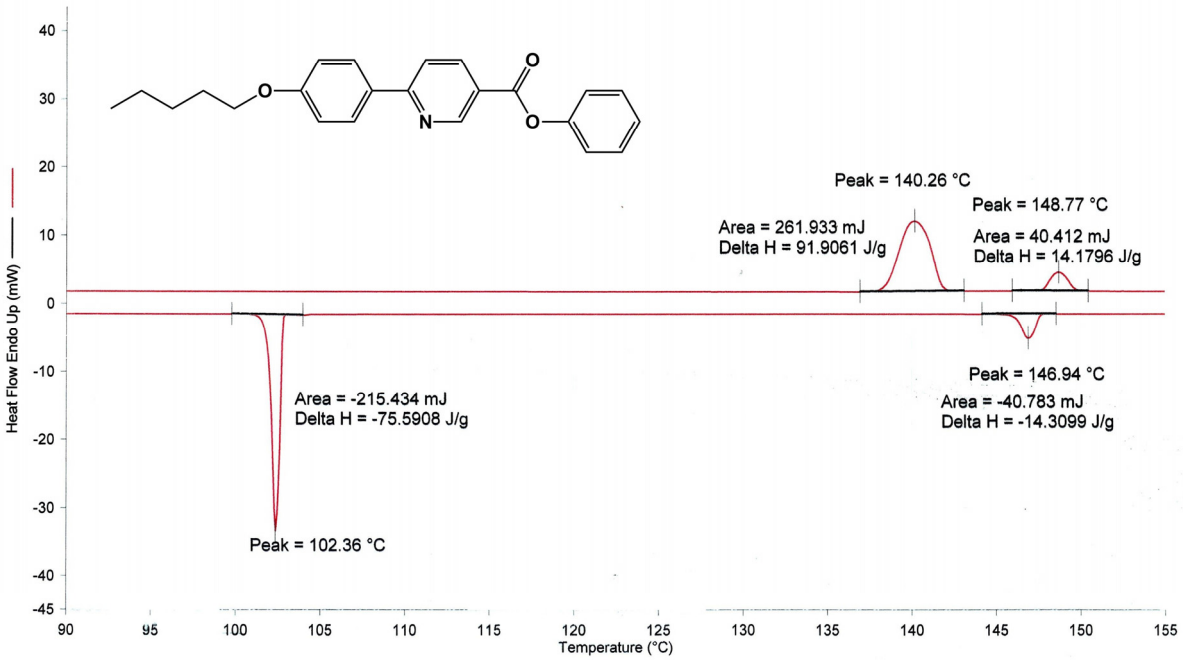
Entry(n)	Phase transition temperatures (ºC) and their corresponding transition enthalpies (KJ mol^{-1})	
	Heating	Cooling
4a (n=3)	Cr 161.7(38.5) I	I 148.5(38.1) Cr
4b (n=4)	Cr 159.4(31.3) I	I 149.7(5.1) S_A 144.9(28.7) Cr

4c (n=5)	Cr 140.3(33.2) S_A 148.8(5.1) I	I 146.9(5.2) S_A 102.4(27.6) Cr
4d (n=6)	Cr 128.5(23.7) S_A 149.8(4.3) I	I 148.2(4.3) S_A 95.34(20.8) Cr
4e (n=7)	Cr 118.3(27.7) S_A 149.4(5.7) I	I 147.9(5.6) S_A 90.32(23.7) Cr

[a] Cr = crystalline phase, S_A = smectic A phase, I = isotropic phase.

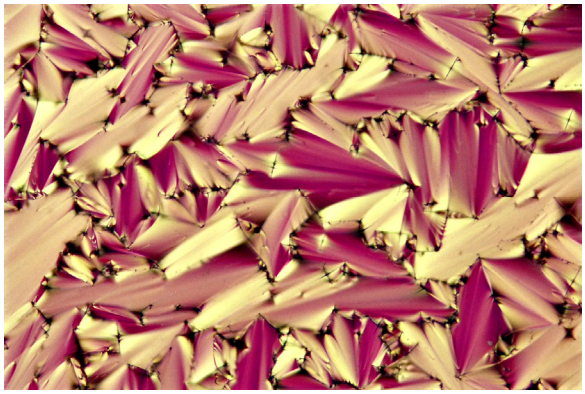
A representative DSC thermogram of 5OPNicP is shown in Figure 1. In the cooling process two exothermic peaks were observed at 146.9 ºC and 102.4 ºC, while two endothermic peaks were observed at 140.3 ºC and 148.8 ºC in the second heating process. This phase transition behaviour was also observed for the second cooling and third heating processes.

Figure 1. Heating and cooling thermograms of 5OPNicP were determined by the second scans at a rate of 5 ºC min^{-1} from differential scanning calorimetry



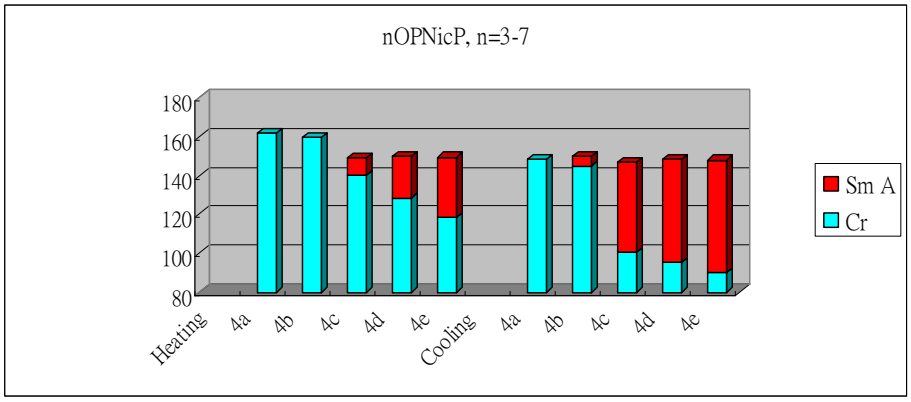
The mesophases of the homologues of phenyl 6-(4-alkoxyphenyl)nicotinates were identified by observing the optical textures under a polarized optical microscope (POM) with two crossed polarizers. No mesophase was observed for 3OPNicP, monotropic smectic A phase was observed for 4OPNicP, enantiotropic smectic A phase was observed for 5OPNicP, 6OPNicP and 7OPNicP. Apparently smectic A phase, presented in Figure 2, was the only liquid crystalline phase observed in the series of nOPNicP compounds.

Figure 2. Polarized optical micrograph of smectic A texture of phenyl 6-(4-hexoxyphenyl)nicotinate 6OPNicP arises from isotropic phase on cooling to 108.8 ºC with magnification of ×100



In the series of nOPNicP compounds the mesophase-to-crystal transition temperatures were drastically decreased between n = 4 and n = 5 and formed an exponentially dropping curve as the series is ascended whereas the mesophase-to-isotropic transition temperatures varied only slightly at around 150 ºC. Conversely, an increase in the mesomorphic range was observed as the series is ascended (Figure 3). During the heating process no smectic phase observed at the lower members can be attributed to their high melting transition temperatures of 3OPNicP and 4OPNicP.

Figure 3. Plot of transition temperatures as a function of terminal alkyl chain length for compounds of nOPNicP, n = 3-7 during heating and cooling at 5 ºC min^{-1}



The corresponding benzene analogues, especially those cyano-substituted phenyl 4'-alkoxy-[1,1'-biphenyl]-4-carboxylates, present nematic mesophase.[11] It is known that in the smectic layer, dipole moments acting across the long axes of the molecules will reinforce one another and be of importance in enhancing lateral attraction which retained the smectic phase order.[12] Perhaps it is the

dipoles from both pyridine and ester functional groups within the nicotine mesogen causing the enhanced lateral attraction and forming preferably the smectic A phase.

In conclusion, a homologous series of nicotine containing liquid crystalline compounds, phenyl 6-(4-alkoxyphenyl)nicotinates (nOPNicP, n = 3-7), was synthesized. Their phase transition behaviours were investigated. Smectic A phase was the only liquid crystalline phase observed in the series of nOPNicP compounds. The nicotinate group in the mesogen provides a strong dipole moment preferentially in the lateral direction relative to the molecular axis and increases intermolecular lateral interactions, leading to the generation of solely smectic A phase.

EXPERIMENTAL

All chemicals and solvents were reagent grades from Aldrich Chemical Co. Anhydrous solvents and chemicals were freshly distilled before use. Silica gel (MN Kieselgel 60, 70-230 mesh) was used for column chromatography. The chemical structures of the compounds were analyzed by ^{1}H and ^{13}C-NMR spectra using a Brucker AC 300 spectrometer. Infrared spectra were carried out on a Perkin-Elmer 1600 Series spectrometer. The purity of the compounds was checked by thin-layer chromatography and further confirmed by elemental analysis.

Mesophases were chiefly identified by examination of the microscopic texture of samples sandwiched between two glass-plates under a polarizing optical microscope (POM) (Olympus BH-2) equipped with a Mettler FP90/FP82HT hot stage. Crossed polarizers were used. Phase transition temperatures and their corresponding transition enthalpies were determined by differential scanning calorimetry (DSC) using a Perkin-Elmer DSC 7 calorimeter at a scan rate of 5 ºC min^{-1}.

General Procedure for the synthesis of phenyl 6-(4-alkoxyphenyl)nicotinates

For **3d**: To a (Grignard) solution of 1-bromo-4-hexoxybenzene (10 mmol) in THF (20 mL) was added freshly dried magnesium granules (11 mmol) under an inert atmosphere. The Grignard solution **1** was then slowly added by syringe into a preformed solution of phenyl nicotinium chloride **2**, which was prepared from phenyl chloroformate (10 mmol) and phenyl nicotinate (10 mmol) in dry THF (20 mL) at -20 ºC, for half an hour. The resulting solution was warmed slowly to rt and stirred for another 8 h. After evaporating the THF, the residue was extracted with Et_2O. The organic layer was further washed once with 20% aqueous NH_4Cl solution and twice with distilled water and brine and dried with magnesium sulfate. For **4d** (6OPNicP): To a solution of dry toluene (20 mL) and crude **3d** was added about 1.5eq. *o*-chloranil. The reaction mixture was heated to reflux for about 3 h under inert atmosphere and then quenched by adding 1N NaOH solution (25 mL) and Et_2O (25 mL) and filtered through celite. Normal aqueous work up and isolation with column chromatography (CH_2Cl_2: hexane = 2.5:1) affords an overall good yield of phenyl 6-(4-hexoxyphenyl)nicotinate **(4d)** (75%). The crude **4d,** 6OPNicP, was further

purified by re-crystallisation several times from EtOAc. Other homologues in nOPNicP series were synthesized essentially by the same procedure as that described above for the n=6 homologue. Very good yields (71%-80%) from this short two-step process were obtained (Table 1). All compounds gave satisfactory data from ^{1}H-NMR, ^{13}C-NMR, ir and elemental analysis as illustrated below.

Phenyl 6-(4-propoxyphenyl)nicotinate (**4a**)

^{1}H-NMR ($CDCl_3$): δ 9.40 (d, 1H, J = 1.5 Hz), 8.44 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.1 Hz), 8.07 (d, 2H, J = 9.0 Hz), 7.81 (d, 1H, J = 8.4 Hz), 7.46 (t, 2H, J = 7.8 Hz), 7.17-7.37 (m, 3H), 7.03 (d, 2H, J = 8.7 Hz), 4.00 (t, 2H, J = 6.6 Hz), 1.75-1.95 (m, 2H), 1.07 (t, 3H, J = 7.5 Hz). ^{13}C-NMR ($CDCl_3$): ppm 163.9, 161.3, 160.9, 151.1, 150.7, 138.7, 130.0, 129.6, 129.1, 126.2, 123.0, 121.7, 119.2, 115.0, 69.8, 22.6, 10.6. IR (KBr): cm^{-1} 2984, 2960, 2931, 2874, 1725, 1591, 1490, 1254, 1190, 1015, 836, 771. Anal. Calcd for $C_{21}H_{19}NO_3$: C, 75.66; H, 5.74; N, 4.20. Found: C, 75.54; H, 5.79; N, 4.14.

Phenyl 6-(4-butoxyphenyl)nicotinate (**4b**)

^{1}H-NMR ($CDCl_3$): δ 9.43 (d, 1H, J = 1.8 Hz), 8.50 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.1 Hz), 8.10 (d, 2H, J = 9.0 Hz), 7.86 (d, 1H, J = 8.4 Hz), 7.47 (t, 2H, J = 8.1 Hz), 7.17-7.37 (m, 3H), 7.04 (d, 2H, J = 9.0 Hz), 4.05 (t, 2H, J = 6.6 Hz), 1.75-1.95 (m, 2H), 1.45-1.60 (m, 2H), 1.00 (t, 3H, J = 7.5 Hz). ^{13}C-NMR ($CDCl_3$): ppm 163.7, 161.6, 160.5, 150.7, 150.6, 139.2, 129.7, 129.2, 126.3, 123.2, 121.7, 119.6, 115.2, 68.0, 31.3, 19.3, 13.9. IR (KBr): cm^{-1} 2960, 2931, 2870, 1721, 1588, 1463, 1252, 1187, 1015, 830, 773. Anal. Calcd for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03. Found: C, 75.95; H, 6.15; N, 3.96.

Phenyl 6-(4-pentoxyphenyl)nicotinate (**4c**)

^{1}H-NMR ($CDCl_3$): δ 9.46 (d, 1H, J = 1.8 Hz), 8.58 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.1 Hz), 8.15 (d, 2H, J = 9.0 Hz), 7.91 (d, 1H, J = 8.4Hz), 7.46 (t, 2H, J = 8.1 Hz), 7.17-7.37 (m, 3H), 7.06 (d, 2H, J = 9.0 Hz), 4.05 (t, 2H, J = 6.6 Hz), 1.75-1.95 (m, 2H), 1.35~1.55 (m, 4H), 0.95 (t, 3H, J = 7.2 Hz). ^{13}C-NMR ($CDCl_3$): ppm 160.6, 155.2, 146.8, 137.2, 136.0, 134.5, 130.1, 129.2, 128.4, 128.2, 126.9, 120.1, 115.0, 68.2, 29.0, 28.2, 22.5, 14.0. IR (KBr): cm^{-1} 2963, 2942, 2869, 1726, 1583, 1468, 1247, 1165, 1014, 833, 776. Anal. Calcd for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88. Found: C, 76.47; H, 6.42; N, 3.82.

Phenyl 6-(4-hexoxyphenyl)nicotinate (**4d**)

^{1}H-NMR ($CDCl_3$): δ 9.41 (d, 1H, J = 1.8 Hz), 8.46 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.1 Hz), 8.08 (d, 2H, J = 9.0 Hz), 7.83 (d, 1H, J = 8.4 Hz), 7.46 (t, 2H, J = 8.1 Hz), 7.17-7.37 (m, 3H), 7.03 (d, 2H, J = 9.0 Hz), 4.04 (t, 2H, J = 6.6 Hz), 1.75-1.90 (m, 2H), 1.30~1.55 (m, 6H), 0.92 (t, 3H, J = 6.9 Hz). ^{13}C-NMR ($CDCl_3$): ppm

161.0, 154.6, 145.9, 137.0, 136.7, 134.9, 129.3, 128.9, 128.7, 128.5, 127.0, 120.6, 115.1, 68.3, 31.6, 29.3, 25.8, 22.7, 14.9. IR (KBr): cm^{-1} 2957, 2941, 2871, 1731, 1586, 1471, 1253, 1175, 1015, 833, 775. Anal. Calcd for $C_{24}H_{25}NO_3$: C, 76.77; H, 6.71; N, 3.73. Found: C, 76.72; H, 6.70; N, 3.65.

Phenyl 6-(4-heptoxyphenyl)nicotinate (**4e**)

^{1}H-NMR ($CDCl_3$): δ 9.44 (d, 1H, J = 1.8 Hz), 8.52 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.8 Hz), 8.13 (d, 2H, J = 8.7 Hz), 7.88 (d ,1H, J = 8.4 Hz), 7.46 (t, 2H, J = 7.8 Hz), 7.17-7.37 (m, 3H), 7.05 (d, 2H, J = 8.7 Hz), 4.07 (t, 2H, J = 6.6 Hz), 1.75-1.95 (m, 2H), 1.25-1.60 (m, 8H), 0.90 (t, 3H, J = 6.6 Hz). ^{13}C-NMR ($CDCl_3$): ppm 160.7, 155.1, 146.6, 137.1, 136.3, 134.6, 129.8, 129.2, 128.5, 128.3, 127.0, 120.2, 115.0, 68.3, 31.8, 29.3, 29.1, 26.1, 22.7, 14.1. IR (KBr): cm^{-1} 2942, 2922, 2856, 1734, 1591, 1471, 1246, 1165, 1013, 837, 776. Anal. Calcd for $C_{25}H_{27}NO_3$: C, 77.09; H, 6.99; N, 3.60. Found: C, 77.00; H, 7.00; N, 3.57.

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