FACILE SYNTHESIS OF A SERIES OF 2-(4-ALKYLOXYPHENYL)-5-CYANOPYRIDINE LIQUID CRYSTALLINE COMPOUNDS

Win-Long Chia[*] and Yu Wei Cheng

Department of Chemistry, Fu Jen Catholic University, Taipei, Taiwan, Republic of China

[*]Corresponding author. Tel: 2-29053567; Fax: 2-29023209;

E-mail: 027087@mail.fju.edu.tw

Abstract – This study describes the facile synthesis of a homologous series of pyridine-containing liquid crystalline 2-(4-alkyloxyphenyl)-5-cyanopyridines (nOPPyCN, n = 3-7). The subject liquid crystals were prepared in a short two-step reaction. First, 4-alkyloxyphenylmagnesium bromides were added to *N*-phenyloxycarbonyl-3-cyanopyridinium chloride, affording a 1,2-dihydropyridine, which was then oxidized by *o*-chloronil. The resulting products, 2-(4-alkyloxyphenyl)-5-cyanopyridines, were obtained in good yields (72%-83%). Thermotropic behaviors of these liquid crystals were investigated using differential scanning calorimetry (dsc) and polarized optical microscopy (pom).

INTRODUCTION

At least ten different liquid crystal material parameters must be optimized to achieve optimal TN-LCD and STN-LCD display performance. Because a single liquid crystal shows at best one or two distinguished properties, mixtures consisting of up to twenty or more polar and weakly polar compounds have to be developed for a given application. In view of the growing need for more advanced displays in the future, therefore, there is a high demand for new nematic liquid crystals and molecular synthesizing methodologies.[1]

Although a plethora of prefunctionalized aromatic compounds are jointed by metal catalyzed C-C coupling reactions developed for the syntheses of biaryls and homologous, only a few of them are applicable to the synthesis of heteroarenes.[2] In many instances, the scope of these reactions suffers from low yields, expensive catalyst requirement, separation from homo-coupled products, and the limitations of the functional groups that are affected.[3]

In former years, some pyridine containing liquid crystalline compounds were synthesized.[4-7] Certain pyridine-containing liquid crystalline compounds have shown enhanced properties in display

applications.[8] Previously, we prepared various 2- or 4-substituted pyridines and alkaloids by regioselective addition of organometallic reagents to 1-acylpyridinium salts.[9] With the simple Grignard reagent and pyridine reactivity enhancement strategy, we have successfully applied this methodology in preparing liquid crystalline 2-(4-alkylphenyl)-5-substituted pyridines.[10] In this paper, facile synthesis of a homologous series of liquid crystalline 2-(4-alkyloxyphenyl)-5-cyanopyridines (nOPPyCN, n = 3-7) **4** is reported (**Scheme 1**).
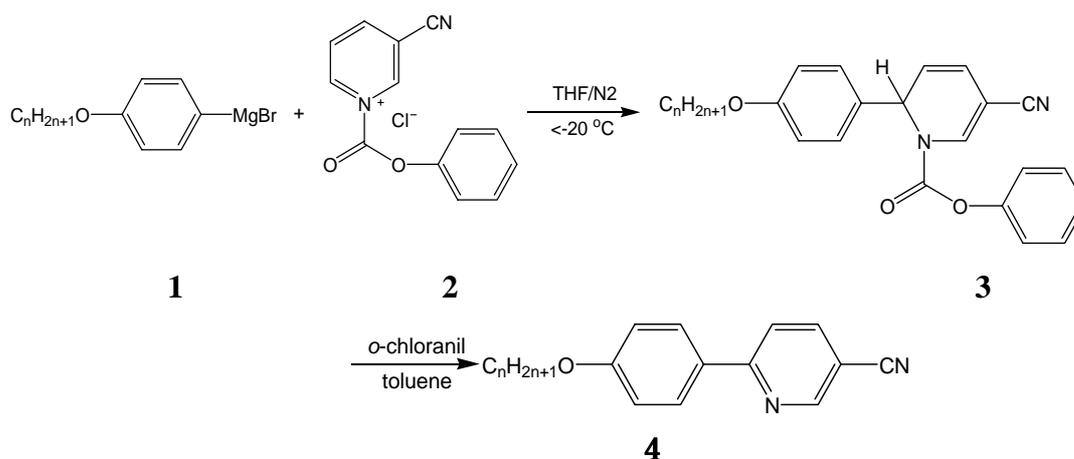
Scheme 1

RESULTS AND DISCUSSION

2.1 Synthesis of 2-(4-alkyloxyphenyl)-5-cyanopyridines(nOPPyCN, n = 3 to 7) :

Except for famous liquid crystalline compound *p*-pentyl-cyanobiphenylene(5CB),[11] *p*-heptyloxy-cyanobiphenylene(7OCB) is also one of the major components in commercially available liquid crystalline compound E7.[12] Therefore, the pyridine analogue of 7OCB would be a fascinating molecule to investigate. However, a tedious process of four synthetic steps for the preparation of 2-(4'-alkyloxyphenyl)-5-cyanopyridines (nOPPyCN) was previously developed by Pavelyuchenko *et al*.[13] The overall yields from the four synthetic steps were poor (12%-24%) and an expensive metal, palladium, was necessary and there were side products produced in the last reduction step.

In this research, Grignard reagent 4-alkyloxyphenylmagnesium bromides (prepared from commercial readily available 4-hydroxy-bromobezene) **1** were reacted with *N*-phenyloxycarbonyl-3-cyanopyridinium chlorides **2** to afford a 1,2-dihydropyridine **3** that was then oxidized by *o*-chloronil, providimg a valuable approach to the synthesis of liquid crystalline 2-(4-alkyloxyphenyl)-5-cyanopyridines (nOPPyCN) **4**, in which the alkyloxy varied from *n*-propyloxy to *n*-heptyloxy (**Scheme 1**). The overall synthetic process was completed in two-steps with very good yields (72%-83%) of 2-(4-alkyloxyphenyl)-5-cyanopyridines (nOPPyCN) obtained (**Table 1**). Highly pure products can be obtained by re-crystallization several times

Table 1. Synthesis of 2-(4-alkyloxyphenyl)-5-cyanopyridines **4a-4e**

Entry	**Alkyl**	Yield[a](%)
4a	propyl	80
4b	butyl	83
4c	pentyl	78
4d	hexyl	72
4e	heptyl	76

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

It is known that nucleophilic attack of a Grignard reagent and its regioselectivity on the pyridine ring can be greatly enhanced by phenyl chloroformate, even in the presence of a cyano group on the ring.[14] -Regioselectivity of the pyridine ring by Grignard reagent attack was found to be overwhelmingly dominant by this synthetic method. Trace amounts of g-addition product (2-3%) can be easily separated from the major -addition product using simple liquid chromatography (hexane : methylene choloride = 1:2) due to high polarity difference of these two compounds. Preparation of other homologous series pyridine-containing liquid crystalline compounds was undertaken.

2.2 Thermotropic behavior of 2-(4-alkyloxyphenyl)-5-cyanopyridines:

Thermotropic behaviors of 2-(4-alkyloxyphenyl)-5-cyanopyridines (nOPPyCN, n = 3-7) we synthesized were investigated using differential scanning calorimetry (dsc) and polarized optical microscopy (pom). The mesomorphic phase transition temperatures from the heating cycle were found to be identical to those reported by Pavelyuchenko *et al.*[13] In addition, the phase transition temperatures of 2-(4'-alkyloxyphenyl)-5-cyanopyridines (nOPPyCN, n = 3-7) from the cooling cycle and their transition enthalpies are reported herein (**Table 2**). It is assumed that entropy changes at T_{N-I} transition are dominated by intermolecular degrees of freedom in the nematic phase.[15] A trend of increasing DS_{N-I} (J K^{-1} mol^{-1}), 0.4052, 0.4789, 0.4886, 0.6176, 0.7559 for nOPPyCN, n = 3 to 7 respectively, is found, which indicates that the longer the rod-like molecules is, the more ordered structure exists in the mesophase, therefore, more orientational entropy changes have to occur at T_{N-I} transition as alkyl chain length increases. From pom study, it shows that nematic phase is mainly the mesophase in this homologue (**Figure 1**), except a smectic phase appearing in 2-(4'-heptyloxyphenyl)-5-cyanopyridines (nOPPyCN, n = 7).

Table 2. Transition temperatures (°C) and corresponding transition enthalpies (kJ mol^{-1}), in parentheses, for homologous series of nOPPyCN, n = 3-7 were determined by the second scans at a heating and cooling rate of 5°C min^{-1} from DSC

Entry	T_{Cr-N}[a] $[T_{C-S}]$	T_{S-N}	T_{N-I}	T_{I-N}	T_{N-S}	T_{N-Cr} $[T_{S-C}]$
4a	93.6	-	97.2	95.6	-	76.1
(n=3)	(15.06)		(0.15)	(0.24)		(11.55)
4b	91.6	-	102.9	101.3	-	64.9
(n=4)	(15.27)		(0.18)	(0.24)		(18.28)
4c	59.2	-	95.4	93.8	-	35.9
(n=5)	(18.28)		(0.18)	(0.21)		(23.39)
4d	62.4	-	99.4	97.8	-	32.7
(n=6)	(23.31)		(0.23)	(0.32)		(31.92)
4e	[58.4]	88.6	97.4	95.6	87.0	[43.2]
(n=7)	(16.02)	(0.17)	(0.28)	(0.38)	(0.079)	(19.37)

[a] Cr = crystalline phase, S = smectic phase, N = nematic phase, I = isotropic phase

There is a ready explanation for the odd-even effect of the T_{N-I} values.[16] It has been found for many homologous series of liquid crystals that the odd carbon atom alkyl chain has a terminal Me group which extends the long molecular axis, whereas in an even number carbon chain the terminal Me group tends to lie off axis. In our study, the corresponding alkyloxy substituted series, the oxygen is equivalent to a CH$_2$ group and a reverse situation has been found, although the alternation of the T_{N-I} values is not great.

Figure 1. Polarized optical micrograph of nematic Schlieren texture of 2-(4'-propyloxyphenyl)-5-cyanopyridines (**4a**) **nOPPyCN, n = 3** arises from crystalline phase on heating to 97°C with magnification of × 100
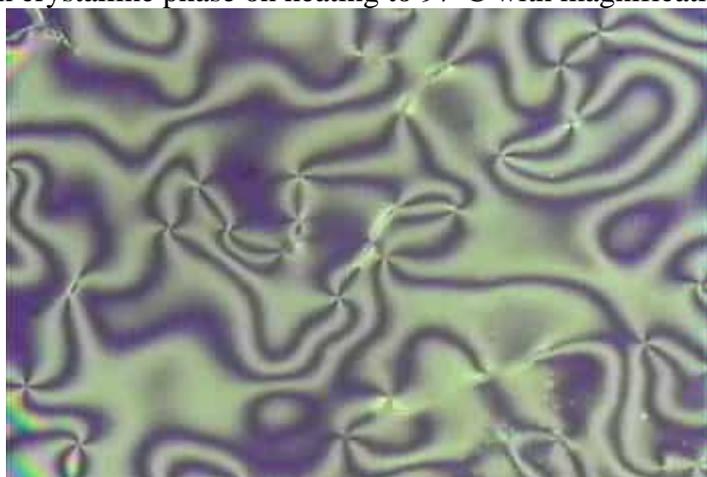
It would be very interesting to compare the mesomorphic transitions of 2-(4-alkyloxyphenyl)-5-cyanopyridines (nOPPyCN, n = 3-7) with those of p-alkyloxy-cyanobiphenylene(nOCB, n = 3-7),[17] since such comparison could not be found elsewhere. The comparison data (**Table 3**) shows that replacement of the relatively nonpolar biphenyl core by more polar phenylpyridine moiety enhances not only the early

appearance of smectic phase (nOPPyCN, n = 7) but also that of nematic phase (nOPPyCN, n = 3, 4). Although it is known that the pyridine ring system with lone pairs of electrons on the nitrogen atoms acts to broaden the molecule and introduces attractive forces which aid smectic formation,[18] contrary to the conventional point of view, it also promotes the early appearance of the enantiotropic nematic phase and provides wider nematic phase ranges and gives higher T_{N-I} values. This indicates that a fine tuned polarity of core structure could allow lowering the number of carbon atoms in the flexible chain and also enhancing its nematic stability.

Table 3. Transition temperatures (°C) for 2-(4-alkyloxyphenyl)-5-cyanopyridines (nOPPyCN, n = 3-7) and p-alkyloxy-cyanobiphenylene(nOCB, n = 3-7)

Compounds	n=3	n=4	n=5	n=6	n=7
nOPPyCN	93.6/-/97.2	91.6/-/102.9	59.2/-/95.4	62.4/-/99.4	58.4/88.6/97.4
nOCB	74.5/-/(64)[b]	78/-/(75.5)[b]	48/-/68	57/-/75.5	54/-/74

[a] All data are listed in a sequence of $T_{Cr-S, N or I}$ / T_{S-N} / T_{N-I}
[b] Values in the bracket indicate monotropy

EXPERIMENTAL

All chemicals and solvents were reagent grades from Aldrich Chemical Co. Anhydrous solvents and chemicals were freshly distilled before use. The ^{1}H and ^{13}C-NMR spectra were recorded on a Brucker AC 300. Infrared spectra were carried out on a Perkin-Elmer 1600 Series. Thermographs were carried out on a Perkin-Elmer DSC 7 Series, calibrated with pure indium. Polarizing optical microscopy was carried out on an Olympus BH-2 equipped with a Mettler FP90/FP82HT hot stage. All phase transitions were measured with a scan rate of 5°C min^{-1}.

General Procedure for the Synthesis of 2-(4-Alkyloxyphenyl)-5-Cyanopyridines.

For **3a**: To a (Grignard) solution of 1-bromo-4-propyloxybenzene (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 3-cyanopyridinium chloride **2**, which was prepared from phenyl chloroformate (10 mmol), 3-cyanopyridine (10 mmol) in dry THF (20 mL) at -20°C, 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$_2$O. The organic layer was further washed once 20% aqueous NH$_4$Cl solution and twice with distilled water and brine and dried with magnesium sulfate. Yields of the intermediates were found to be around 90%. For **4a**: To a solution of dry toluene (20 mL) and crude **3a** was added about 1.5eq. of o-chloranil. The reaction mixture was heated to reflux for about 3 h under inert atmosphere and then quenched by adding 1N NaOH (25 mL) and Et$_2$O (25 mL) and

filtered through Celite. Normal aqueous work up and isolation with column chromatography (hexane : CH_2Cl_2 = 1:2) affords very good yield of 2-(4-propyloxyphenyl)-5-cyanopyridines (**4a**) (79.7%). The crude products **4a** were further purified by recrystallization several times from Et_2O and *n*-hexane. All compounds gave satisfactory data from ^{1}H-NMR, ^{13}C-NMR, ir and elemental analysis as illustrated below.

2-(4-Propyloxyphenyl)-5-cyanopyridines (4a)

^{1}H-NMR (CDCl$_3$): d 8.88 (d, 1H, *J*=2.1 Hz), 8.00 (d, 2H, *J*=9 Hz), 7.94 (dd, 1H, *J$_1$*=8.4 Hz, *J$_2$*=2.1Hz), 7.76 (d, 1H, *J*=8.4 Hz), 7.01 (d, 2H, *J*=9 Hz), 3.99 (t, 2H, *J*=6.6 Hz), 1.90-1.78 (m, 2H), 1.06 (t, 3H, *J*=7.5Hz). ^{13}C-NMR (CDCl$_3$): ppm 161.5, 160.1, 152.4, 139.7, 129.5, 128.9, 119.0, 117.3, 115.0, 106.8, 69.7, 22.5, 10.5. IR (KBr): cm^{-1} 3049, 2966, 2937, 2874, 2221, 1587, 1469, 1247, 1015, 832. Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H 5.92; N 11.76. Found: C, 75.63; H, 5.93; N, 11.74.

2-(4-Butyloxyphenyl)-5-cyanopyridines (4b)

^{1}H-NMR (CDCl$_3$): d 8.89 (d, 1H, *J*=2.1 Hz), 8.01 (d, 2H, *J*=9 Hz), 7.95 (dd, 1H, *J$_1$*=8.4 Hz, *J$_2$*=2.1 Hz), 7.78 (d, 1H, *J*=8.4 Hz), 7.01 (d, 2H, *J*=9 Hz), 4.04 (t, 2H, *J*=6.6 Hz), 1.85-1.76 (m, 2H), 1.58-1.45 (m, 2H), 0.99 (t, 3H, *J*=7.5 Hz). ^{13}C-NMR (CDCl$_3$): ppm 161.6, 160.1, 152.4, 139.7, 129.5, 129.0, 119.1, 117.2, 115.1, 106.9, 68.0, 31.3, 19.3, 13.9. IR (KBr): cm^{-1} 3055, 2956, 2936, 2871, 2224, 1587, 1471, 1246, 1006, 829. Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.12; H, 6.44; N, 11.09.

2-(4-Pentyloxyphenyl)-5-cyanopyridines (4c)

^{1}H-NMR (CDCl$_3$): d 8.89 (dd, 1H, *J$_1$*=2.1 Hz, *J$_2$*=0.9 Hz), 8.01 (d, 2H, *J*=9 Hz), 7.95 (dd, 1H, *J$_1$*=8.4 Hz, *J$_2$*=2.1 Hz), 7.78 (d, 1H, *J*=8.7 Hz), 7.01 (d, 2H, *J*=9 Hz), 4.03 (t, 2H, *J*=6.3 Hz), 1.87-1.77 (m, 2H), 1.52~1.32 (m, 4H), 0.94 (t, 3H, *J*=7.2 Hz). ^{13}C-NMR (CDCl$_3$): ppm 161.5, 160.1, 152.4, 139.7, 129.5, 128.9, 119.1, 117.2, 115.0, 106.8, 68.3, 28.9, 28.2, 22.5, 14.0. IR (KBr): cm^{-1} 3057, 2965, 2938, 2858, 2229, 1588, 1470, 1249, 1017, 832. Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.68; H, 6.83; N, 10.52.

2-(4-Hexyloxyphenyl)-5-cyanopyridines (4d)

^{1}H-NMR (CDCl$_3$): d 8.88 (dd, 1H, *J$_1$*=2.1 Hz, *J$_2$*=0.6 Hz), 8.01 (d, 2H, *J*=9 Hz), 7.93 (dd, 1H, *J$_1$*=8.4 Hz, *J$_2$*=2.1 Hz), 7.76 (d, 1H, *J$_1$*=8.4 Hz, *J$_2$*=0.6 Hz), 7.01 (d, 2H, *J*=9 Hz), 4.03 (t, 2H, *J*=6.6 Hz), 1.86-1.77 (m, 2H, *J*=7.8 Hz), 1.53-1.43 (m, 2H), 1.40-1.32 (m, 4H), 0.93 (t, 3H, *J*=6.9 Hz). ^{13}C-NMR (CDCl$_3$): ppm 161.5, 160.2, 152.4, 139.6, 129.6, 128.9, 119.0, 117.3, 115.0, 106.8, 68.3, 31.6, 29.2, 25.7, 22.6, 14.0. IR

(KBr): cm^{-1} 3053, 2950, 2925, 2855, 2225, 1589, 1471, 1249, 1020, 824. Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.07; H, 7.20; N, 9.97.

2-(4-Heptyloxyphenyl)-5-cyanopyridines (4e)

^{1}H-NMR (CDCl$_3$): d 8.89 (d, 1H, J=2.1 Hz), 8.01 (d, 2H, J=8.7 Hz), 7.95 (dd, 1H, J_1=8.4 Hz, J_2=2.1 Hz), 7.77 (d, 1H, J=8.4 Hz), 7.00 (d, 2H, J=8.7 Hz), 4.02 (t, 2H, J=6.6 Hz), 1.86-1.77 (m, 2H), 1.50-1.31 (m, 8H), 0.90 (t, 3H, J=6.6 Hz). ^{13}C-NMR (CDCl$_3$): ppm 161.5, 160.1, 152.3, 139.8, 129.4, 129.0, 119.1, 117.2, 115.0, 106.8, 68.3, 31.8, 29.2, 29.1, 26.0, 22.6, 14.1. IR (KBr): cm^{-1} 3071, 2953, 2930, 2855, 2235, 1593, 1471, 1249, 1046, 820. Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.40; H, 7.55; N, 9.48.

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