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# Solid-phase synthesis of liquid crystalline isoxazole library

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**Abstract**—Combinatorial library of isoxazoles was prepared by 1,3-dipolar cycloaddition on solid support. *p*-Cyano derivatives showed nematic and/or smectic A phases. A bilayer smectic phase for **2h** is proposed by the combination of molecular mechanics calculation and X-ray diffraction experiment.

Liquid crystalline materials have received great attention for a wide variety of applications. Numerous liquid crystalline compounds have been synthesized so far. Some of them represent rod-like shapes, which are a well-known class of typical liquid crystalline compounds, showing smectic and nematic mesophases derived from the self-organization of their anisometric units.[1] 3,5-Disubstituted isoxazole liquid crystalline compounds[2] are in the class of rod-shaped molecules, which exhibit classical nematic and smectic mesophases even though the molecules have a bent core rather than a rod-like core. Structure–property relationships in isoxazole liquid crystals still remain fairly uncharted. Unsymmetrical diphenyl isoxazoles bearing an alkoxy chain at one end of the molecules and a polar group at the other are interesting mesogens because a polar group affects their mesomorphic behaviors. However, 3,5-diphenyl isoxazoles having a polar group are not well investigated.[3] We set out to study the mesomorphic behaviors of anisometric isoxazole-based compounds **1** and **2** having a cyano group as a polar functionality.

Intermolecular interaction of the flexible hydrophobic chains on the benzene ring is a key factor to stabilize the liquid crystalline phase. A variety of the alkyl chain has to be examined until liquid crystalline phase appears. It remains a time-consuming task to find the desired compound. Combinatorial chemistry is one of the most promising approaches to accelerate the discovery process of desired functional molecules.[4] In particular, solid-phase combinatorial chemistry has gained a momentum in the field of not only chemistry but also material science, and has become a major tool for searching desired functional compounds. Recently, liquid crystalline libraries of troponoid[5] and benzenoid[6] amides were prepared on solid support. In this paper, we report the solid-phase synthesis of the liquid crystalline isoxazole library and its mesomorphic properties.

Our strategy for the synthesis of the isoxazole liquid crystals on solid support is outlined in Figure 1. Phenyl acetylene unit is immobilized on a polymer support by the amide linkage, which can be easily cleaved by acid catalysis and converted to the cyano group.[7,8] 1,3-Dipolar cycloadditions of nitrile oxides are well documented and provide efficient entries to the synthesis of isoxazoles. The cycloaddition on solid support[8] with nitrile oxides having a variety of alkoxy substituents provides the isoxazole library, which can allow us to carry out the systematic evaluation for the liquid crystallinity.

Parallel synthesis of the isoxazole library on solid support was carried out by using parallel synthesizer MiniBlock.[9] Rink resin **3** was selected as a solid support. Free amine **4**, prepared from **3** by removal of the Fmoc group, was subjected to a condensation reaction of ethynylbenzoic acid **5** or **6** with *N*,*N′*-diisopropylcarbodiimide and 1-hydroxybenzotriazole to afford

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*Keywords*: Combinatorial chemistry; Liquid crystal; Isoxazole; 1,3-Dipolar cycloaddition; Solid-phase synthesis.

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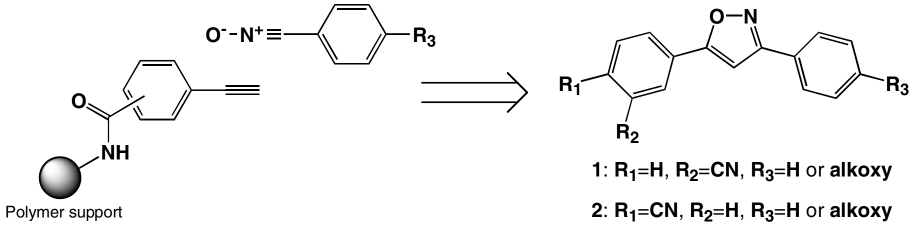


**Figure 1.** Synthetic strategy of isoxazole liquid crystal on solid support.

condensate **7**. The corresponding nitrile oxides were generated in situ from hydroximinoyl chlorides **8** with triethylamine, which were quickly reacted with the triple bond of resin **7** to produce solid-attached diphenyl isoxazole **9**. $Tf_2O$ worked nicely to cleave the linkage to liberate desired isoxazoles **1** or **2** into the solution.[7] After quick purification of the crude products by column chromatography on $SiO_2$, the isoxazoles were furnished in good yield. Yields of all compounds are listed in Table 1. All of the compounds were characterized by $^1H$ NMR spectroscopy and high-resolution mass spectrometry. Purities of all the products were confirmed by $^1H$ NMR (>95%) (Scheme 1).

Thermal behavior of compounds **1a**–**2k** was investigated by differential scanning calorimetry (DSC) and polarized optical microscopy. Transition temperatures are shown in Table 1. Mesomorphic behaviors were found in compounds **2b**–**k** whereas compounds **1a**–**k** and **2a** were not mesomorphic.

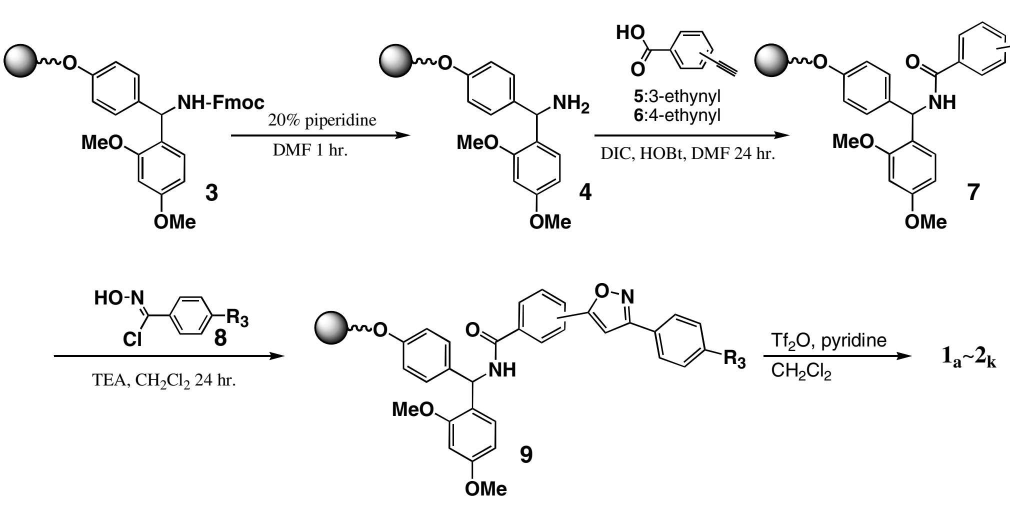
This should be due to the larger molecular dipole of compounds **2** produced by the presence of the cyano group at *para*-position. The CN group of compounds **1** made molecular breadth wider to decrease the thermal stability of mesophases. The presence of the alkoxy groups is substantial for the formation of liquid crys-

**Table 1.** Yields and transition temperatures of compounds **1** and **2**

| | $R_3$ | Yield (%) | Transition temperature (°C)[a] | | $R_3$ | Yield (%) | Transition temperature (°C)[a] |
|---|---|---|---|---|---|---|---|
| **1a** | H | 98 | Cr•172•Iso | **2a** | H | 67 | Cr•195•Iso |
| **1b** | $OCH_3$ | 72 | Cr•159•Iso | **2b** | $OCH_3$ | 90 | Cr•144•N•213•Iso |
| **1c** | $OC_2H_5$ | 85 | Cr•157•Iso | **2c** | $OC_2H_5$ | 83 | Cr•128•N•199•Iso |
| **1d** | $OC_3H_7$ | 49 | Cr•138•Iso | **2d** | $OC_3H_7$ | 82 | Cr•138•(SmA•120•)N•191•Iso |
| **1e** | $OC_4H_9$ | 64 | Cr•131•Iso | **2e** | $OC_4H_9$ | 66 | Cr•126•N•185•Iso |
| **1f** | $OC_5H_{11}$ | 77 | Cr•116•Iso | **2f** | $OC_5H_{11}$ | 83 | Cr•115•N•180•Iso |
| **1g** | $OC_6H_{13}$ | 61 | Cr•112•Iso | **2g** | $OC_6H_{13}$ | 69 | Cr•112•N•178•Iso |
| **1h** | $OC_7H_{15}$ | 88 | Cr•109•Iso | **2h** | $OC_7H_{15}$ | 67 | Cr•114•SmA•160•N•180•Iso |
| **1i** | $OC_8H_{17}$ | 62 | Cr•110•Iso | **2i** | $OC_8H_{17}$ | 58 | Cr•113•SmA•168•N•176•Iso |
| **1j** | $OC_9H_{19}$ | 71 | Cr•114•Iso | **2j** | $OC_9H_{19}$ | 74 | Cr•92•SmA•176•Iso |
| **1k** | $OC_{10}H_{21}$ | 65 | Cr•112•Iso | **2k**[b] | $OC_{10}H_{21}$ | 68 | Cr•93•SmA•173•Iso |

[a] Cr, crystal; N, a nematic phase; SmA, a smectic A phase; Iso, isotropic liquid. The transition temperatures were recorded by DSC during the first heating process.

[b] A mixture of compound **2k** and its regioisomer was reported.[3]



**Scheme 1.**

talline phases. There are two mesomorphic phases observed in a series of compounds **2**. Shorter chained compounds **2b–g** displayed a nematic phase whereas a smectic phase was observed in longer chained compounds **2j** and **2k**. Mesomorphic behaviors are thus dependent on the chain length of $R_3$.[1] Extension of the alkyl chain of **2** gave rise to a smectic A phase in which the molecules are more ordered than in a nematic phase. In order to investigate the structure of the molecular array in the smectic A phase for **2h**, X-ray diffraction measurement at 140 °C was carried out. A sharp peak at $2\theta$ (2.87°), characteristic of the interlayer periodicity, gave the layer spacing $d$ value of 30.8 Å, which is obviously larger than the calculated molecular length (20 Å) of **2h**.

Fortunately, a single crystal of **2h** was obtained. The X-ray crystallography[10] disclosed the antiparallel orientation of two rigid cores due to the strong dipole–dipole interaction between the cyano groups (Fig. 2). This gave us an important insight into the molecular array of the liquid crystalline phase. The antiparallel orientation allows us to propose a bilayer smectic A mesophase, typically found in many mesogens incorporating strong polar terminal groups.

Molecular modeling based on the crystal structure with MacroModel V6.5 using Amber* force field[11] gave the layer spacing, about 27–30 Å. A plausible bilayer smectic A phase is shown in Figure 3. The calculated value is consistent with the layer space $d$ given by the X-ray diffraction.

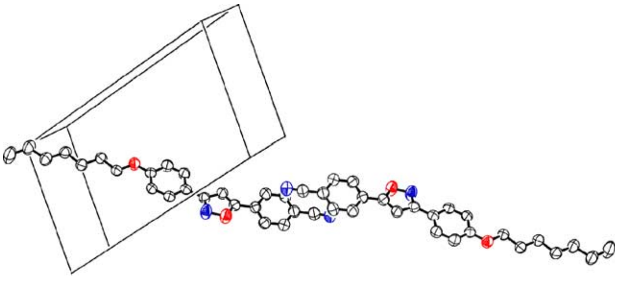


**Figure 2.** Crystal structure of compound **2h**.

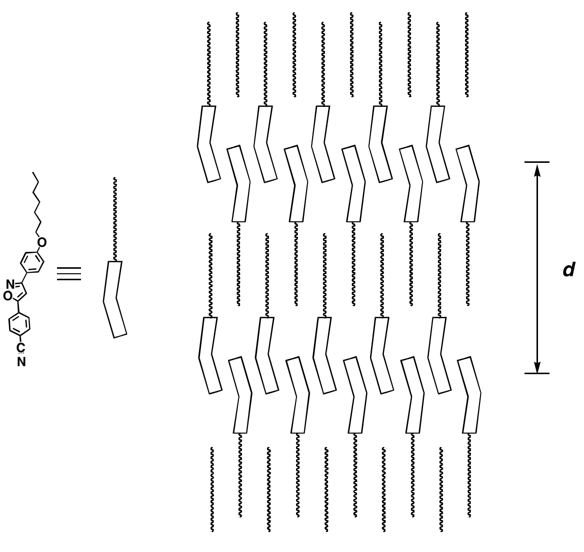


**Figure 3.** Proposed bilayer structure of **2h** in a smectic A phase.

In conclusion, we constructed the liquid crystalline isoxazole library based on 1,3-dipolar cycloaddition. The systematic investigation of the liquid crystalline isoxazoles reveals that the alkyl side chains of the isoxazole and the position of the polar cyano group plays an important role for the production of the liquid crystalline phases.

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9. Personal synthesizer MiniBlock is supplied by Mettler Toledo Co. Ltd.
10. Crystallographic data for **2h**: $C_{23}H_{24}N_2O_2$, FW = 360.45, triclinic, space group $P\bar{1}$, $a = 5.7310(2)$ Å, $b = 9.7650(5)$ Å, $c = 18.387(1)$ Å, $\alpha = 100.235(2)°$, $\beta = 93.032(2)°$, $\gamma = 97.182(4)°$, $V = 1001.70(9)$ Å$^3$, $T = 293$ K, and $Z = 2$; of 4094 total unique reflections, 2955 were considered observed at the level of $|F_0| > 3.0\sigma|F_0|$. The structure was solved by the direct method (Sir 92). Full-matrix least squares refinements converged to a conventional $R$ factor of 0.057, $wR = 0.254$, GOF = 1.30. Supplementary crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, UK as supplementary publication number CCDC No. 226886.
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